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STEREOCHEMICAL STUDIES OF ANTIMUSCARINIC AGENTS

BY



WAYNE KENNETH JEFFERY

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Stereochemical Studies of Antimuscarinic Agents" submitted by Wayne Kenneth Jeffery in partial fulfilment of the requirements for the degree of Master of Science.

ABSTRACT

A review of the possible role of conformational isomerism in the physiological actions of atropine is given. The pharmacological effects of esters of N-methyl-3- and 4-piperidinol is reviewed. Some new anticholinergic compounds based on:

1. N-methyl-3-piperidinol
2. N-methyl-4-piperidinol
3. 1,3-dimethyl-4-piperidinol
4. 1,2,5-trimethyl-4-piperidinol

as the amino alcohol, and benzoic and diphenylacetic acid as the esterifying agent are described.

PMR characteristics of the compounds synthesized are reported and interpreted in terms of configuration and conformation. The results of testing of these compounds for their anticholinergic activity by their inhibition of contraction of the guinea pig ileum induced by acetylcholine; by their mydriatic action on the mouse pupil, and by their inhibition of tremors induced by oxotremorine in the mouse, are given.

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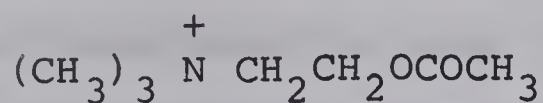
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INTRODUCTION AND LITERATURE

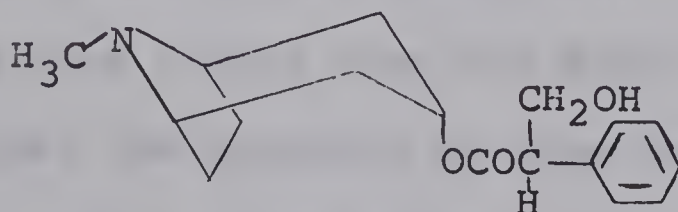
Antimuscarinic drugs inhibit the action of acetylcholine (Ach (1)) on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to



1

acetylcholine but lack cholinergic innervation. Antimuscarinic agents are highly selective antagonists of muscarinic agents on smooth and cardiac muscle and exocrine gland cells. Antimuscarinic agents have a wide variety of pharmacological actions: small doses cause slight cardiac slowing and higher doses cause an increase in heart rate; dryness of the mouth, inhibition of sweating, mydriasis, cycloplegia, antitremor activity and inhibition of the gastrointestinal tract may occur. However, not all anti-muscarinic agents cause all of the above actions, as some drugs are more specific for one action than another, and many of the above pharmacological actions, specifically spasmolysis and mydriasis, are dose dependent.

Atropine (2), the best known cholinergic antagonist, is the racemic form of hyoscyamine, the (-)-tropyl ester of 3- α -tropanol.



2

Atropine is a competitive antagonist (Goodman and Gillman, 1965) of acetylcholine at the cholinergic receptor; therefore, atropine may be assumed to bear some chemical relationship to acetylcholine such that it can combine with the receptor and block the action of acetylcholine on the receptor. The relationship between atropine and acetylcholine is not obvious at first sight, but there is a resemblance in that both molecules possess an ester function which is separated from a charged nitrogen atom by a carbon chain.

Atropine offers three interesting stereochemical features, namely: 1) the chirality of the tropic acid moiety, 2) the relative configuration of the N-Methyl and OCOR features, and 3) the conformation of the piperidine ring.

Pharmacological comparisons between atropine (\pm hyoscyamine), (-)-hyoscyamine and (-)-hyoscine (the latter is an atropine analog in which the bimethylene bridge carries an epoxide function) have been reviewed by Barlow (1964). It is to be noted that most of the antimuscarinic activity lies in the levo isomer (see Table I).

Long et al. (1956) compared (-)-hyoscyamine and the (+)-camphor-10-sulfonate and found the (+) isomer to be virtually inactive, while Bovet (1948) found that (-)-hyoscyamine was 10 - 100 times more active than the dextro analog. Beckett (1959) summarized the activity of some dextro and levo isomers of synthetic spasmolytics containing an asymmetric

centre and found that the (-) isomer is always more active than the (+) isomer (see Table II). Maffi et al. (1960) also noticed a marked specificity of action in the (+) and (-) isomers of tropyl α -methyl tropate; the (-)/(+) potency ratio being 50. This stereospecificity is lost if the acid portion of the molecule does not contain an asymmetric centre. It is therefore evident that the most important part of the molecule in antimuscarinic agents is the acid portion and not the amino alcohol. This is evident in the α -methyl-tropyl esters of β -methylcholine (Ellenbroek et al., 1965). The (-) enantiomer is more active than the (+) enantiomer, and the β -methylcholine configuration has a relatively small influence on activity (see Table III).

TABLE I

BLOCKING ACTIVITY OF COMPOUNDS RELATED TO ATROPINE

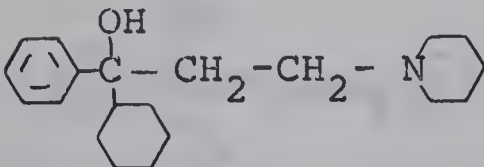
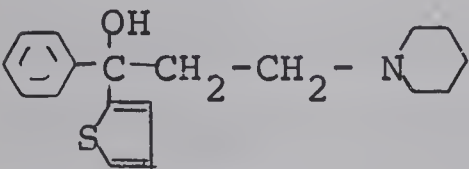
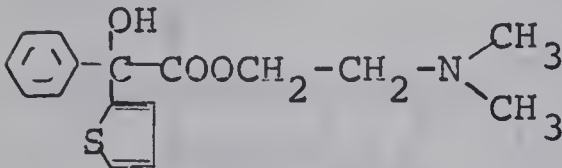
(Barlow 1964)

Compound	Equipotent molar ratios relative to atropine				
	Cat Salivation	Cat Blood Pressure	Cat Eye	Mouse Eye	Guinea Pig Ileum
(-) Hyoscyamine	0.65	0.53	0.5	0.54	0.31
(+) Hyoscyamine	11.00	12.00	-	-	10.00
(-) Hyoscine	0.73	0.83	0.07-0.1	0.20	1.3

TABLE II

ACTIVITY OF ISOMERS WITH SPASMOLYTIC ACTIVITY

(Beckett 1959)

Structure	Activity			
	Relative cholinolytic activity on rabbit ileum [(-)-hyosciamine = 100]			
	(-)	47.0		
	(+)	0.3		
	(-)	30.0		
	(+)	1.0		
	(+)	at least X4 activity of (-)		
<hr/>				
	<u>Relative activity (atropine = 1)</u>			
	<u>Mydriasis</u>	<u>Guinea Pig Ileum</u>		
HCl	(-)	0.06	(-)	0.10
	(+)	0.003	(+)	0.002
MeI	(-)	0.62	(-)	1.6
	(+)	0.01	(+)	0.01
EtI	(-)	0.76	(-)	1.0
	(+)	0.004	(+)	0.0034

continued

TABLE II (continued)

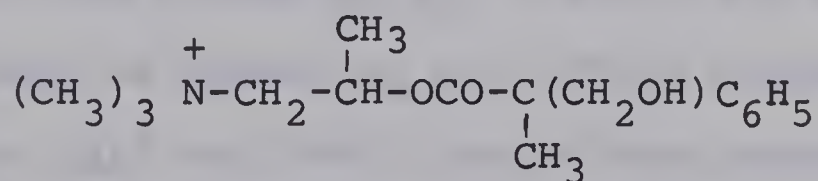
		<u>Relative activity (atropine = 1)</u>			
		<u>Mydriasis</u>		<u>Guinea Pig Ileum</u>	
<chem>Oc1ccccc1C(C2CCCCC2)CCN3CCCCC3</chem>	HCl	(-) 0.12	(-) 0.71		
		(+) 0.025	(+) 0.075		
	MeI	(-) 1.1	(-) 0.86		
		(+) 0.034	(+) 0.018		
	EtI	(-) 0.41	- - - - -		
		(+) 0.11	- - - - -		
<chem>CN(C)CCOC(=O)C1=CC=CC=C1C2=CC=CC=C2C(C)(C)C</chem>			(-) 50.0		
			(+) 0.3		

TABLE III

ANTICHOLINERGIC POTENCY OF ISOMERIC α -METHYLTROPYL

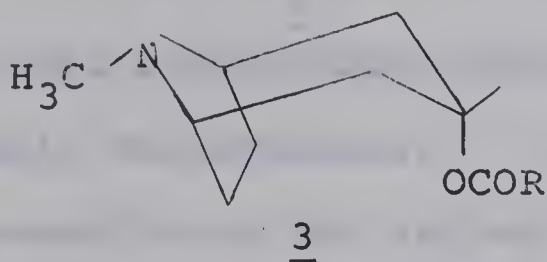
ESTERS OF β -METHYLCHOLINE

(Ellenbroek et al. 1965)



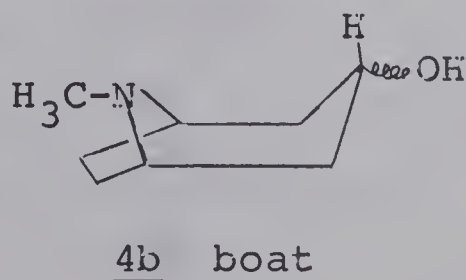
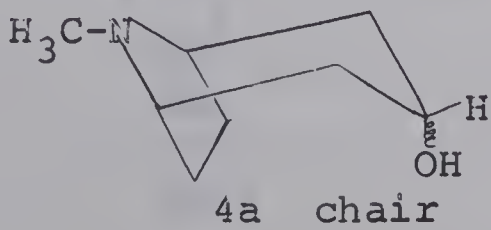
<u>Configuration</u>		<u>Relative Affinity (atropine = 1)</u>
parent acid	parent choline	
(-)	R	0.25
(-)	S	1.3
(+)	R	0.008
(+)	S	0.013

In atropine, the configuration of the N-Methyl/OCOR features is cis, assuming the N-Methyl group to be always equatorial (3). An earlier report by Kierberman

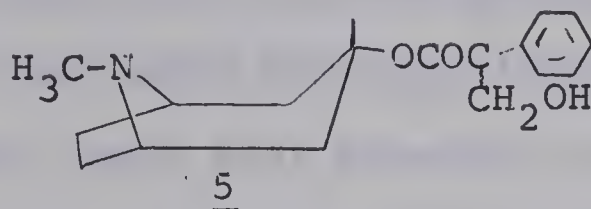


(1892) and more recent findings by Gyermek (1953, 1953a) found the benzoate ester of tropine (cis N-methyl/OCOR) to be more active than the benzoate ester of pseudotropine (trans N-methyl/OCOR). From these results, it appears that a cis orientation of the N-methyl/OCOR in atropine is required for maximum activity. The trans isomers (pseudotropine derivatives) although exhibiting reduced activity are not devoid of activity. A great deal more work on cis-trans pairs of antimuscarinic drugs is needed, as there is not much information in this area.

In assigning the conformation of atropine, reference must be made to work on tropine and pseudotropine. The proton magnetic resonance spectrum (PMR) reported by Chen and LeFevre (1965a) and Bishop et al. (1966), and the X-ray crystallography data of Visser et al. (1954), support the chair conformation (4a) for both tropine and pseudotropine rather than the boat form (4b). In atropine, however, the



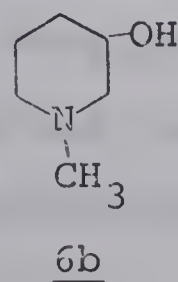
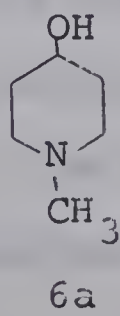
bulky 3-substituent may well favour the boat form (5),



because of increased interactions involving the bimethylene bridge in the chair conformation.

In the present work the aim was to obtain data upon aspects (2) and (3), i.e. the cis-trans pairs, and the conformation of the piperidine ring. We chose to study an isomeric tropine/pseudotropine pair. The acetoxy and the benzilate esters were selected. The acetoxy esters were chosen because they give excellent PMR spectra from which information could be deduced about the configuration and conformation of the molecule. The benzilates were studied because various authors, Brucke (1938), Friedman (1959), Gyorgy (1960), Krietmar (1936) and Kroner (1936), found that the tropine, pseudotropine benzilate esters are all potent antimuscarinic agents.

Derivatives of N-methyl-4-piperidinol were also studied. N-methyl-4-piperidinol (6a) itself may be regarded as a simplified version of the isomeric tropan-3-ols which lacks the 2,6-dimethylene bridge. Esters of both N-methyl-4-piperidinol and its 3-analog (6b) are known to have anti-



muscarinic properties.

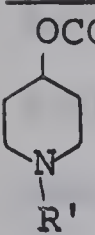
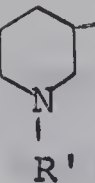
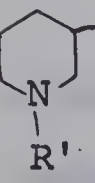
Burtner and Cusic (1943) were the first to synthesize compounds of this type using N-methyl-4-piperidinol as the amino alcohol. They found that N-methyl-4-piperidyl diphenylacetate was a potent antimuscarinic agent, having about 1/10 the activity of atropine. Biel et al. (1952, 1955), and Abood et al. (1959) synthesized compounds of this type using the 3-analog as the amino alcohol (see Table IV). Some of their compounds, i.e. the N-methyl and N-ethyl derivatives of 3-piperidyl benzilate, were as active or more active than atropine in certain pharmacological tests. Many other authors, Coan et al. (1956), Cannon (1960), Biel et al. (1961), Klosa and Delmar (1962) and Kadin and Cannon (1962), have synthesized and tested compounds of this type and found that many of them were antimuscarinics. The most potent of these compounds, the diphenylacetates and the benzilate derivatives, have undergone a series of detailed pharmacological investigations. Chen (1952, 1954, 1954a, 1959), Brimblecombe et al. (1970) and Long and Keasling (1954) found that some of these compounds had a specificity of action, i.e. they would inhibit guinea pig ileum but had a mild effect on salivation and lacrimation at the same dose.

Abood et al. (1958, 1959) and Ostfeld et al. (1958) noticed that these compounds had one side effect that was very interesting; some of these compounds were potent hallucinogens. The interest in these compounds now turned from their parasympatholytic effect to their psychotomimetic

TABLE IV

ANTIMUSCARINIC ACTIVITY OF DERIVATIVES

OF N-METHYL-4-PIPERIDINOL AND ITS 3-ANALOG.

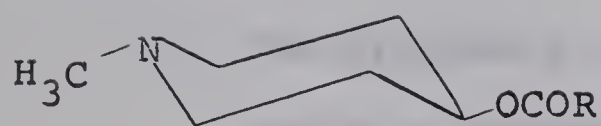
Structure	R	R'	Salt	Pharmacology	Reference
				Reciprocal spas- molytic activity on rabbit intestine	Burtner and Cusic 1943
	(C ₆ H ₅) ₂ CH	CH ₃	HCl	ACh 1.8	Histamine 0.5
	(C ₆ H ₅) ₂ CH	C ₄ H ₉	HCl	100.0	1.5
Atropine				0.14	4.0
				Effective Dilu- tion of drug which inhibits Guinea Pig Ileum by 50% Activity x 10 ⁻⁶ M	Biel et al. 1952
	(C ₆ H ₅) ₂ CH	C ₂ H ₅	HCl		4.0
	(C ₆ H ₅) ₂ CH	CH ₃	HCl		5.0
	(C ₆ H ₅) ₂ COH	C ₂ H ₅	HCl		166.0
	(C ₆ H ₅) ₂ COH	C ₂ H ₅	CH ₃ Br		1000.0
Atropine					500.0
				Inhibition of Guinea Pig Ileum (Atropine = 1)	Biel et al. 1955
	(C ₆ H ₅) ₂ CH	CH ₃	HCl		0.01
	(C ₆ H ₅) ₂ CH	C ₂ H ₅	CH ₃ Br		0.07
	(C ₆ H ₅) ₂ COH	CH ₃	HCl		0.60
	(C ₆ H ₅) ₂ COH	CH ₃	CH ₃ Br		0.50
	CH ₃	CH ₃	CH ₃ I		Stimulation
Transentin					0.01

actions. Many authors, e.g. Abood et al. (1958, 1959, 1961, 1962), Cannon (1960), Biel et al. (1961, 1962) and Kadin and Cannon (1962), tried to correlate psychotomimetic activity with anticholinergic activity. The only conclusions which could be drawn were that all compounds which were hallucinogenic were potent anticholinergics, but not all potent anticholinergics were hallucinogenic; and that the 3-piperidyl esters were the most potent hallucinogens, then the 2-piperidyl esters, and the 4-piperidyl esters which were weakly hallucinogenic (i.e. the 4-piperidyl esters are potent anticholinergics but they have the least psychotic side effects).

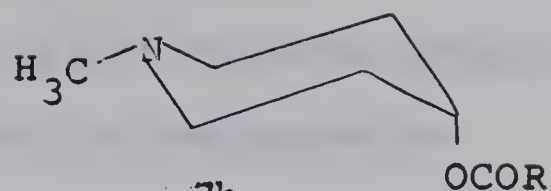
With the wide variety of compounds synthesized a number of structure activity relationships have been determined. These have been reviewed by Abood (1962) and Biel et al. (1962).

Some of the more important relationships are (1) the position of the ester side chain varies the effect as explained above; (2) substitution in the acid portion or the piperidine portion of the ester decreases activity; (3) the benzilic acid esters are more potent than the diphenylacetic acid esters; (4) quaternization of the nitrogen usually leads to an increase in activity.

The N-Me/OCOR geometry in the N-methyl-4-piperidinols is almost certainly trans (7a), being the preferred conformation rather than the cis (axial OCOR) conformation (7b). PMR evidence is given later in the thesis which confirms this.

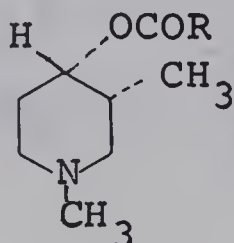


7a



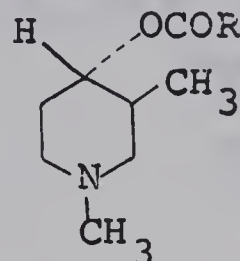
7b

Introduction of a 3-methyl group would lead to cis and trans 3-Me/4-OCOR isomers (8).



cis

8

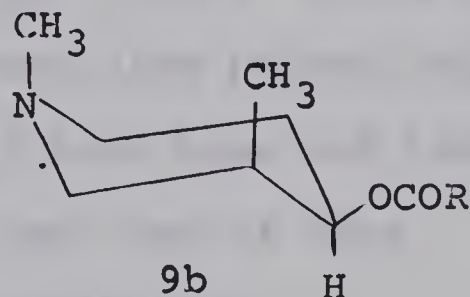


trans

The preferred conformation of the cis isomer may well be the axial OCOR (conformation (9a) which is equivalent to atropine),

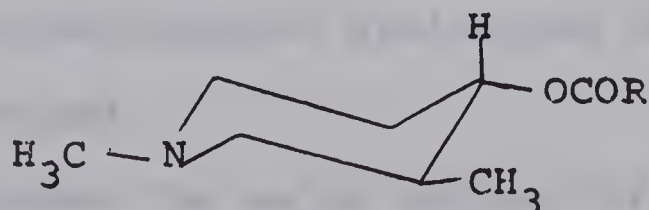


9a



9b

but this needs to be established. The preferred conformation of the trans isomer is almost certainly the equatorial OCOR (10), because the corresponding inverted chair carries two

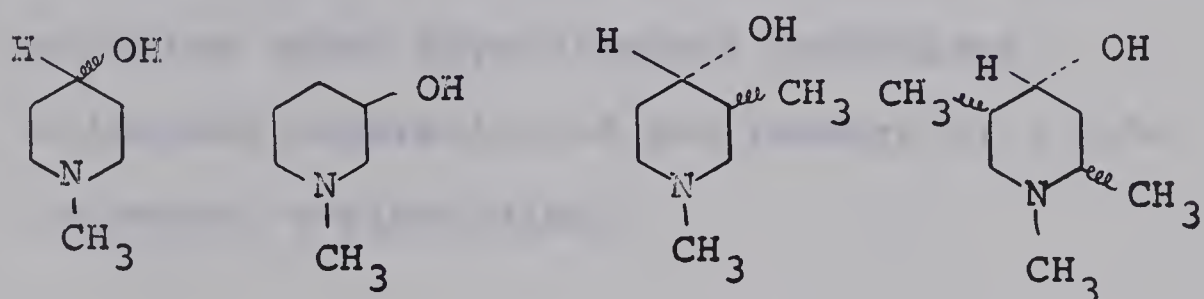


10

axial substituents. Hence, esters of cis and trans 1,3-dimethyl-4-piperidinol may well provide isomeric pairs comparable to the tropyl esters of tropine and pseudotropine.

The following investigation was therefore undertaken.

1. The synthesis of esters (likely to have cholinolytic properties) of the following amino alcohols (11).



11

The esters were synthesized from diphenylacetic acid and benzilic acid. Burtner and Cusic (1943) found that the diphenylacetates are quite potent cholinolytics, and Biel et al. (1961) found that the benzilate derivatives were also potent cholinolytics. Tropic acid would have been the ideal acid to esterify; however, the cost of this chemical made this course prohibitive.

2. The separation of isomers of the esters where appropriate and investigation of their stereochemistry.
3. The pharmacological evaluation of the esters synthesized.

The above three formed the major project of this thesis. Other aspects investigated were as follows.

4. The formation of the acetoxy esters of the amino alcohols for evaluation as muscarinic agents.
5. Formation of esters of tropine and pseudotropine.

6. A preliminary investigation of the synthesis and resolution of the cholinolytic (\pm)-2,2-diphenyl-4-methyl dimethyl-amino-1,3-dioxolane.
7. A PMR study of tropine, pseudotropine, and atropine under physiological conditions.
8. Attempted separation of the isomers of 1,2,5-trimethyl-4-piperidinol.

Figure 1. The first two principal components of the data set.

Figure 2. The first two principal components of the data set.

Figure 3. The first two principal components of the data set.

Figure 4. The first two principal components of the data set.



Figure 7. The first two principal components of the data set.

Variable	PC1	PC2	Variable	PC1	PC2
μ_1	0.95	0.05	μ_2	0.95	0.05
μ_3	0.95	0.05	μ_4	0.95	0.05
μ_5	0.95	0.05	μ_6	0.95	0.05
μ_7	0.95	0.05	μ_8	0.95	0.05
μ_9	0.95	0.05	μ_{10}	0.95	0.05
μ_{11}	0.95	0.05	μ_{12}	0.95	0.05
μ_{13}	0.95	0.05	μ_{14}	0.95	0.05
μ_{15}	0.95	0.05	μ_{16}	0.95	0.05
μ_{17}	0.95	0.05	μ_{18}	0.95	0.05
μ_{19}	0.95	0.05	μ_{20}	0.95	0.05

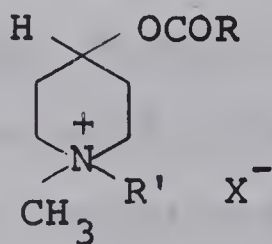
DISCUSSION

The first two principal components of the data set are shown in Figure 1. The first principal component accounts for 95% of the variance in the data, while the second principal component accounts for 5% of the variance.

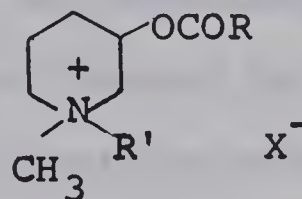
The first two principal components of the data set are shown in Figure 2. The first principal component accounts for 95% of the variance in the data, while the second principal component accounts for 5% of the variance.

I. SYNTHESIS OF ESTERS OF N-METHYL-4-PIPERIDINOL AND ITS
3-HYDROXY ANALOG

The esters (14-25) of type (12) and (13) could be traced in the literature.



12



13

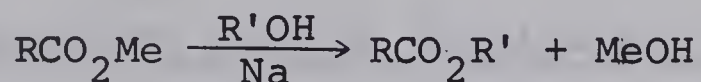
<u>R</u>	<u>R'</u>	<u>X</u>	<u>No.</u>	<u>R</u>	<u>R'</u>	<u>X</u>	<u>No.</u>
CH ₃	H	Cl	<u>14</u>	CH ₃	H	Cl	<u>20</u>
CH ₃	CH ₃	I	<u>15</u>	CH ₃	CH ₃	I	<u>21</u>
(C ₆ H ₅) ₂ CH	H	Br	<u>16</u>	(C ₆ H ₅) ₂ CH	H	Cl	<u>22</u>
(C ₆ H ₅) ₂ CH	CH ₃	I	<u>17</u>	(C ₆ H ₅) ₂ CH	CH ₃	I	<u>23</u>
(C ₆ H ₅) ₂ COH	H	Cl	<u>18</u>	(C ₆ H ₅) ₂ COH	H	Cl	<u>24</u>
(C ₆ H ₅) ₂ COH	CH ₃	I	<u>19</u>	(C ₆ H ₅) ₂ COH	CH ₃	I	<u>25</u>

Compounds (16), (18), (19), (21), (22) and (24) have been synthesized previously (see experimental results for literature data) by various means.

Three general methods have been used to synthesize esters of type (12) and (13): the reaction of the desired chloropiperidine with the free acid, transesterification and the reaction of the acid chloride with the desired amino alcohol. A brief description of the above procedures follows.

In the first procedure the chloropiperidine is added to a hot solution of the acid in isopropanol and the solution is refluxed for 2-12 hours. The crystalline solid which precipitates upon cooling is the desired product. This procedure was used by Burtner and Cusic (1943) to synthesize compound (16). Burtner states that this is an excellent procedure where acid chlorides are unstable or cannot be made.

Many variations of the transesterification procedure are available; the process is as follows (26):



26

Coan et al. (1956) used the third procedure to synthesize compound (15). The amino alcohol and diphenylacetyl chloride were heated to 140°C under nitrogen atmosphere for two hours. The melt was then basified and extracted into ether to yield the crude ester. All procedures reported yields varying from 30-80%. In the present work none of the above procedures were used directly, mainly due to the length and nature of the reaction.

N-Methyl-4-Piperidyl Acetate Hydrochloride (14)

Acetylation of N-methyl-4-piperidinol with acetyl chloride in ethyl acetate produced the title compound in 91% yield as the hydrochloride salt.

N-Methyl-4-Piperidyl Acetate Methiodide (15)

The free base liberated from (14) was dissolved in absolute ethanol and treated with an excess of methyl iodide to yield the title compound in 86% yield.

N-Methyl-3-Piperidyl Acetate Hydrochloride (20)

The same procedure as for the synthesis of compound (14) was used to obtain the title compound in 78% yield.

N-Methyl-3-Piperidyl Acetate Methiodide (21)

The same procedure as for the synthesis of compound (15) was used to obtain the title compound in 90% yield.

N-Methyl-4-Piperidyl Diphenylacetate and Derivatives
(16) and (17)

The preparation of this ester proved to be more difficult than at first thought. Initially the preparation of the title compound was attempted several times by refluxing a benzene solution of equimolar portions of N-methyl-4-piperidinol and diphenylacetyl chloride (26a) for a period of eight hours. The white crystalline product which separated during the reaction was identified by m.p., PMR, IR, and elemental analysis to be the hydrochloride of the amino alcohol. Various other solvents were then tried; Biel et al. (1952) used pyridine-ethyl acetate, but we found this solvent leads to a mixture of products, pyridine hydrochloride, and N-methyl-4-piperidinol hydrochloride. Burtner and Cusic (1943)

found isopropanol to be a very suitable solvent; however, again we obtained the hydrochloride of the amino alcohol when this solvent was employed. The initial procedure was then tried with the addition of 5% pyridine. After eight hours of refluxing, a viscous gum had separated out of the reaction mixture. PMR and IR evidence again showed this to be a mixture of products, pyridine hydrochloride and the hydrochloride of the amino alcohol, and the desired ester. Separation of this mixture was not attempted. The first procedure was repeated again with the addition of a 10% excess of anhydrous sodium carbonate to take up the HCl gas liberated during the reaction. The suspension was heated under reflux for 24 hours and stirred vigorously by a mechanical stirrer for the required time. The sodium carbonate was then filtered off and the benzene evaporated to dryness under reduced pressure. The oil which was obtained was subjected to column chromatography (activated alumina) and eluted with ether. The ether was evaporated to dryness and the PMR of the crude oil was identified as that of the desired compound (29%). The oil was not purified by vacuum distillation due to the small quantity of product which was obtained. Coan et al. (1956) state that the oil obtained crystallizes on standing to yield a crystalline basic ester which has a m.p. of 162°C. Crystallization did not occur after 48 hours, so it was used without any further purification. Burtner and Cusic (1943) found that the hydrochloride salt was very hygroscopic and did not record a melting point. The hydrobromide

salt (16) was then prepared in the usual manner. The hydrobromide salt proved not to be hygroscopic and had a m.p. of 165-166°C. The methiodide (17) was obtained in the usual manner in 87% yield. Due to the poor yield of the previous reaction, a transesterification procedure was attempted to see if the yield could be increased. The procedure of Cannon (1960) was used. Equimolar portions of the amino alcohol and methyldiphenylacetate (27) (synthesized from diphenylacetic acid and methanol in sulfuric acid) and sodium methoxide were heated under reflux for twenty hours. A Dean-Stark apparatus was connected to the reaction flask to collect the side product methanol. By this procedure the yield of the crude ester was increased to 45%. Thus the transesterification procedure gives rise to a larger yield than the acid chloride method.

N-Methyl-3-Piperidyl Diphenylacetate and Derivatives
(22) and (23)

The transesterification procedure as explained under compound (16) was used to yield the title compound in 63% yield. The hydrochloride salt (22) was made in the usual manner, and it was found not to be hygroscopic as was the 4-isomer. The methiodide (23) was synthesized in the usual manner to give a 90% yield of the title compound.

N-Methyl-4-Piperidyl Benzilate and Derivatives (18) and (19)

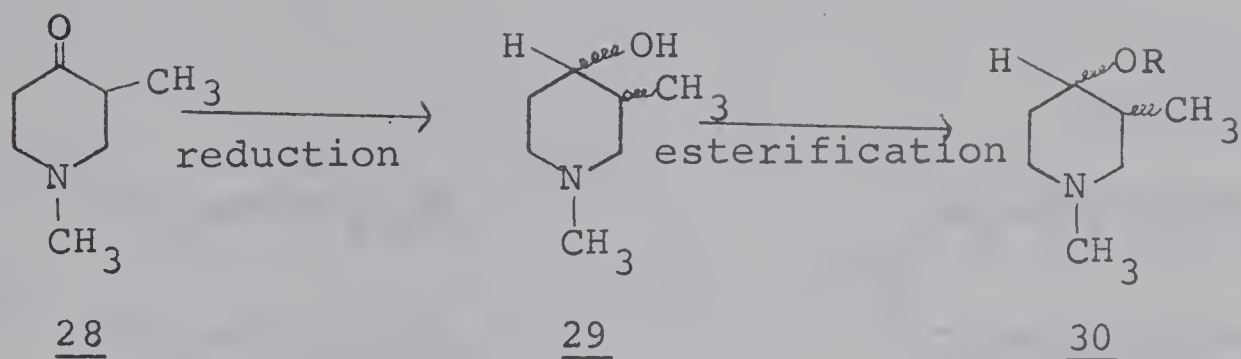
The acid chloride method could not be used here (due to the lability of the hydroxyl group) and the only practical procedure is transesterification. The method of Cannon (1960) was again employed. The yield of the crude ester was 58%. Coan et al. (1953) and Klosa (1962) found that on standing the crude ester solidified and had a melting point of 161-162°C. Again, it was found our crude ester would not solidify, and it was used without any further purification. The hydrochloride (18) was obtained in the usual manner. It had a melting point of 214-215° C which corresponds to the literature value (see experimental results). The methiodide (19) was obtained again by the usual procedure in 87% yield.

N-Methyl-3-Piperidyl Benzilate and Derivatives (24) and (25)

The procedure of Cannon (1960) was again used to obtain the crude ester in 69% yield. Again, due to the small quantities of product obtained, it was used without any further purification. The hydrochloride (24) and the methiodide (25) were obtained in excellent yields by the usual procedures.

II. SYNTHESIS OF 1,3-DIMETHYL-4-PIPERIDONE

In the present investigation 1,3-disubstituted-4-piperidones of type (28) were required since these on reduction yield the isomeric alcohols of type (29), from which by esterification it was proposed to prepare esters of type (30).

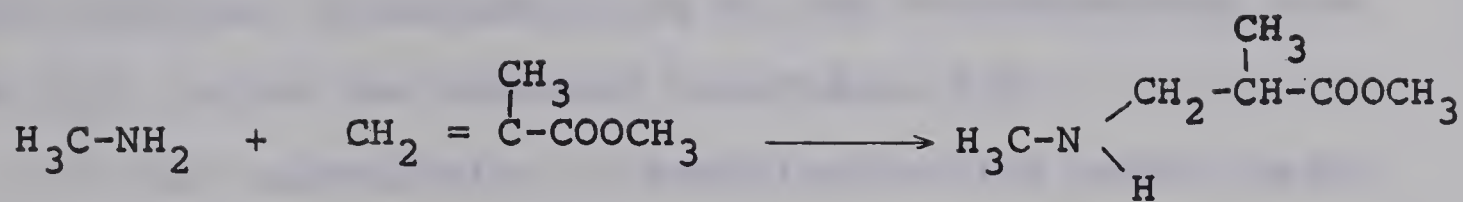


The general method for the preparation of 4-piperidones is illustrated in Scheme I. It depends essentially on the cyclization of the dicarboxylic ester (33) followed by decarboxylation of the resulting β -keto ester (34). The diester (33) may be prepared by condensing a primary amine with ethyl acrylate (Caldwell 1949, McElvain and Rorig 1948), or alternatively using the method employed by earlier workers (Thayer and McElvain 1927) of reacting ethyl-(N-substituted)- β -aminopropionate (31) with ethyl- β -bromopropionate (32) in the presence of silver oxide. The usual Dieckman condensation agents, sodium, sodium alkoxide, or sodamide may be used to effect condensation of the β -keto ester (33). Hydrolysis and decarboxylation of the ester with hydrochloric acid yields the required piperidone (35).

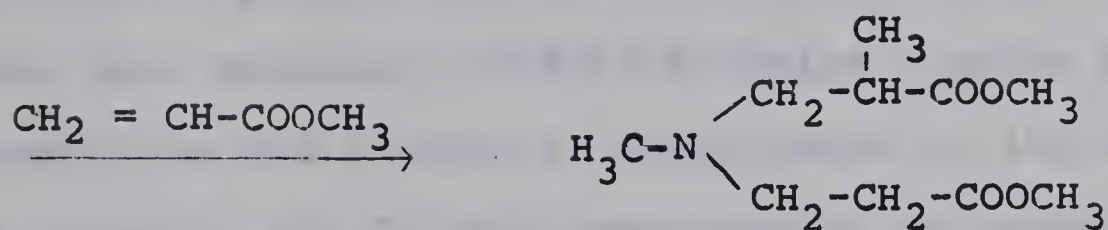
1,3-Dimethyl-4-Piperidone (39)

This piperidone was first prepared by Howton (1945). The method used was a modification of the usual 4-piperidone synthesis; the procedure is outlined in Scheme II. It consists of a Dieckman cyclization of (β -carbomethoxyethyl)-(β -carbomethoxy-N-propyl)methylamine (37) which is prepared by the addition of methylamine to methyl methacrylate and

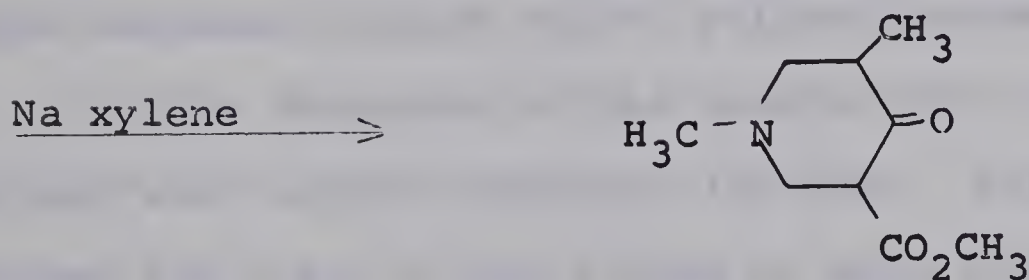
Scheme I General Preparation of Cyclic 4-Piperidones



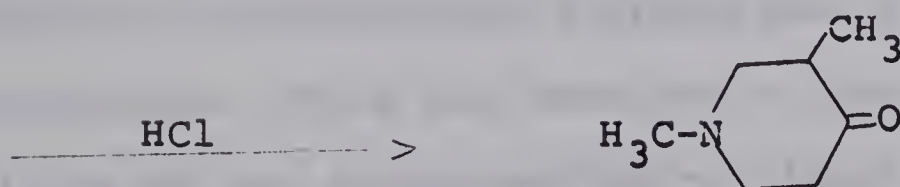
36



37



38



39

Scheme II Synthesis of 1,3-Dimethyl-4-Piperidone

the addition of the resulting secondary amino ester (36) to methyl acrylate. Decarboxylation of the 5-carbomethoxy compound (38) yields the required piperidone (39).

In the condensation of methylamine with methyl methacrylate, the yield varies between 30-50%. The portions of methylamine and methyl methacrylate were varied to try and increase the yield of the secondary amino ester. The best yields were obtained (50-60%) by using 3 moles of methyl methacrylate and 2 moles of methylamine in 400 ml of absolute ethanol, and allowing the mixture to react for three days at room temperature. The slower the methyl methacrylate is added to the methylamine, the better the yield. If the reaction is allowed to sit for more than three days, the yields decrease greatly due to polymerization.

In the formation of the diester (37), the yields obtained were always excellent (85-95%). Kirk (1958) improved the yield of the ketone by acidifying the reaction mixture obtained from the cyclization of the diester (37) with an excess of concentrated hydrochloric acid and refluxing the aqueous phase without attempting to isolate the 1,3-dimethyl-5-carbomethoxy-4-piperidone (38) prior to decarboxylation. This was done due to the slight water miscibility of the 5-carbomethoxy-4-piperidone with water, which makes complete extraction impossible. We found this also to be true.

We further increased the yield in the final step to 40% by a modification of the extraction procedure. Kirk

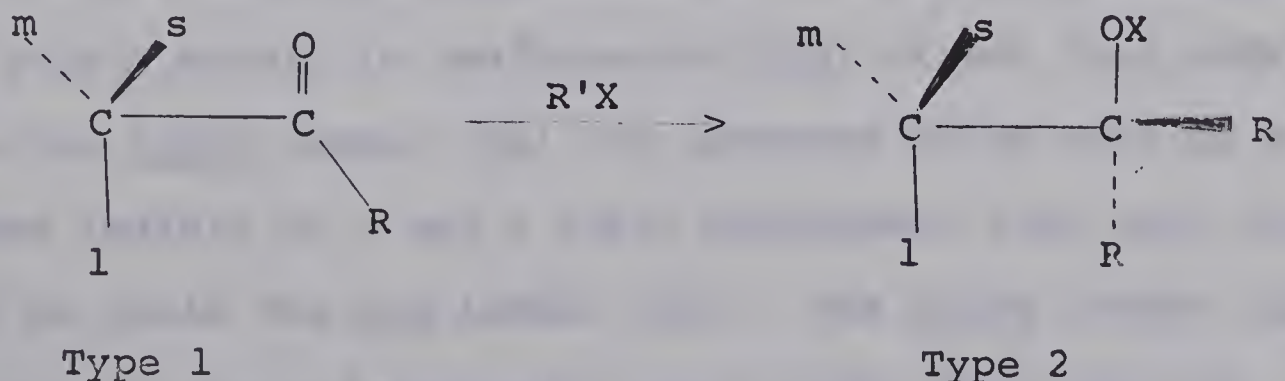
extracted the aqueous phase with ether six times; we found the ketone is slightly miscible with water and complete extraction with this procedure is impossible. A continuous chloroform extractor was set up and allowed to run for 48 hours, whereby near complete extraction was effected.

III. STEREOCHEMISTRY OF REDUCTION OF 1,3-DIMETHYL-4-PIPERIDONE

A. Introduction

Before we discuss the reduction procedure, a brief discussion of the stereochemistry of reduction of ketones will be given.

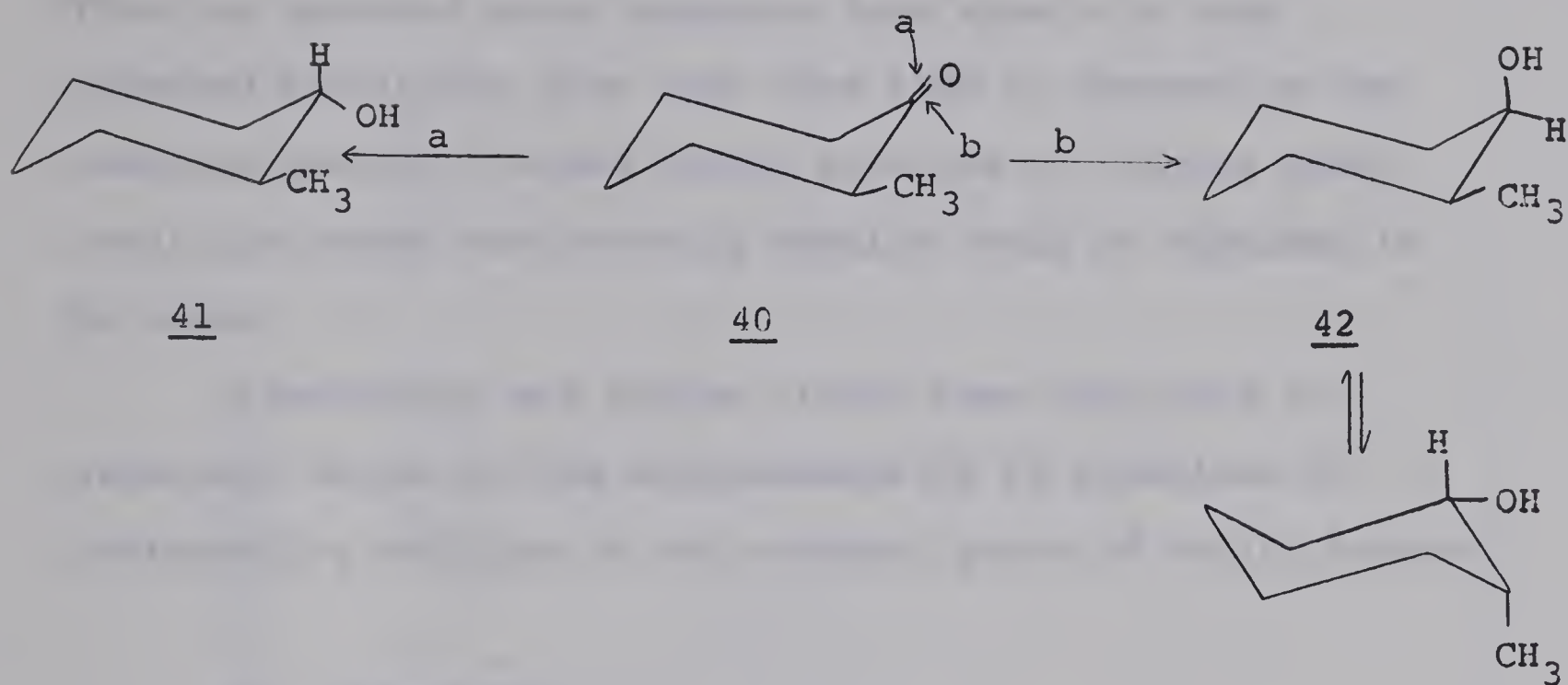
The stereochemical composition of the products obtained from reactions involving addition to the C-atom of a carboxyl group adjacent to an asymmetric centre in aliphatic compounds has been the subject of investigation by many workers. Cram and Elhafez (1952) proposed the following rule from which stereoisomeric composition of the products may be predicted in the reaction of type 1 \longrightarrow type 2: That diastereoisomer will predominate which would be formed by the approach of the entry group R' from the



less hindered side of the double bond (of the carbonyl group) when the rotational conformation of the C---C bond is such that the double bond is flanked by the two least bulky groups (s-m) attached to the adjacent carbon atom. The rule emphasizes the importance of the relative degree of steric hindrance which would be encountered in the two possible directions of approach to the C-atom of the carbonyl group. Thus in the reduction by lithium aluminium hydride, the carbonyl oxygen atom being co-ordinated to the metal atom (AlH_3) becomes effectively the largest group and thus orientates itself between s and m. The approach of the $\text{R}'(\text{H})$ group is then directed from the least hindered side of the molecule.

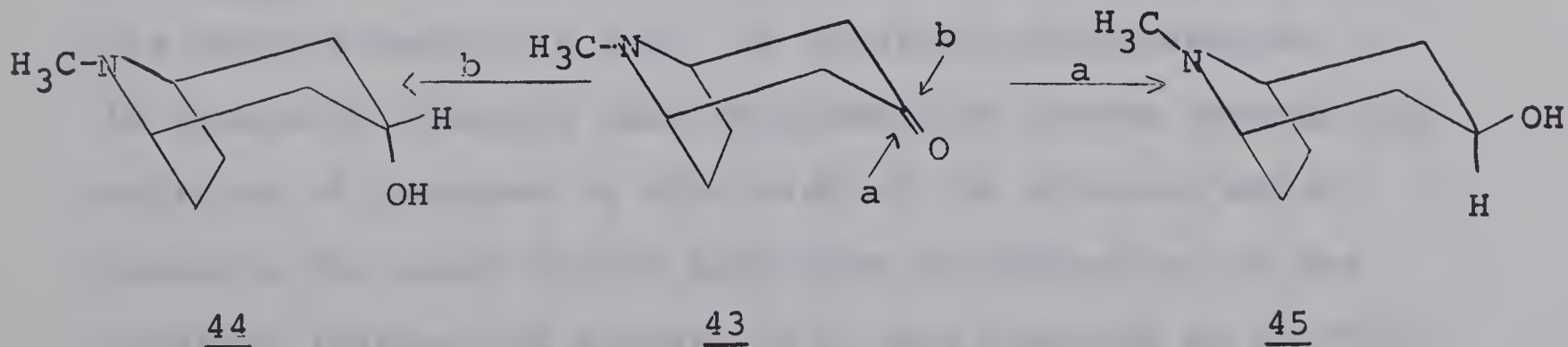
The percentage of each diastereoisomer present in the products obtained from addition to the carbonyl group of a cyclic ketone will depend partly upon the steric hindrance of the carbonyl group, but the relative thermodynamic stabilities of the isomers will also be a significant factor. These two factors will influence the rate of formation of the isomers from the transition complexes, (Dauben et al. 1956) and their importance may be shown by the following examples.

In the catalytic reduction of 2-methylcyclohexanone, which exists mainly in conformation (40), attack from side a, yields the trans isomer (41), an approach which will be more hindered (mainly by 3 and 5 axial hydrogens) than that from side b to yield the cis isomer (42). The trans isomer (41) is, however, thermodynamically more stable than the cis



isomer (42); equilibration of the alcohols yields 99% of the trans isomer (Dauben et al. 1956). The two effects are therefore in opposition and the size of the reducing species will therefore have some effect on the percentage of each diastereoisomer formed.

The reduction of heterocyclic ketones may be considered similarly. Beckett et al. (1959a) have shown that the reduction of tropinone (43) by various reducing agents, yields more of the thermodynamically less stable tropine (44) than was present in equilibrated tropine or pseudotropine (45).



This was expected since approach from side a is less favoured sterically than that from side b; changes in the reducing species yielded larger portions of tropine under conditions where the reducing species would be expected to be large.

Kamernitsky and Akhrem (1962) have published an excellent review on the stereochemistry of reactions of nucleophilic addition to the carbonyl group of cyclic ketones.

B. Literature

Mistryukov (1965 and 1965a) carried out a reduction study, both chemically and catalytically on a number of cyclic ketones including 1,3-dimethyl-4-piperidone. His results are summarized in Table V. Mistryukov follows the hypothesis that if you increase the size of the reducing species you obtain more of the thermodynamically less stable axial alcohol. Thus in reducing 1,3-dimethyl-4-piperidone with sodium borohydride, lithium aluminium hydride and aluminium isopropoxide, you would obtain more of the cis (axial OH) alcohol with aluminium isopropoxide, and more of the trans (equatorial OH) alcohol with sodium borohydride; his results bear this out. In catalytic hydrogenation, it is generally accepted that hydrogenation occurs through cis addition of hydrogen to that side of the molecule which presents the least steric hindrance to adsorption of the catalyst (Farkas and Farkas, 1937, and Linstead et al. 1942). Therefore the least hindered arrangement of the chair form

TABLE V

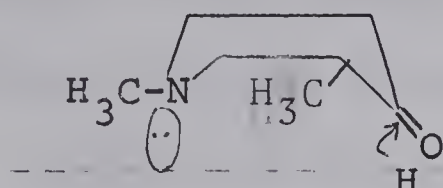
ISOMERIC COMPOSITION OF 1,3-DIMETHYL-4-PIPERIDINOLS

AS OBTAINED BY MISTRYUKOV

Ketone	Form	Reaction Conditions	Reaction e	Products a
1,3-Dimethyl-4-piperidone	Base	$\text{NaBH}_4\text{-H}_2\text{O}$	84	16
1,3-Dimethyl-4-piperidone	CH_3I	$\text{NaBH}_4\text{-H}_2\text{O}$	96	4.0
1,3-Dimethyl-4-piperidone	Base	$\text{LiNH}_3\text{-EtOH}$	98	2.0
1,3-Dimethyl-4-piperidone	Base	Aluminium Isopropoxide	36	64
1,3-Dimethyl-4-piperidone	CH_3I	Aluminium Isopropoxide	49	51
1,3-Dimethyl-4-piperidone	Base	LiAlH_4	64	36
1,3-Dimethyl-4-piperidone	HCl	$\text{Pt/H}_2\text{O}$	69.5	30.5
1,3-Dimethyl-4-piperidone	HCl	Pt/EtOH	69	31
1,3-Dimethyl-4-piperidone	CH_3Cl	$\text{Pt/H}_2\text{O}$	96.6	3.4
1,3-Dimethyl-4-piperidone	Base	Pt/Dioxane	50	50
1,3-Dimethyl-4-piperidone	Base	Pt/EtOH	55	45
1,3-Dimethyl-4-piperidone	Base	$\text{Pt/H}_2\text{O}$	44.3	55.7
1,3-Dimethyl-4-piperidone	Base	$\text{Pt/CH}_3\text{COOH}$	65	35

of the piperidone ring over the catalyst would lead to addition of hydrogen from the equatorial side resulting in the formation of an axial hydroxyl group.

Mistryukov (1965a) found this not to be true for 1,3-dimethyl-4-piperidone using Adams catalyst under pressure with varying solvents. He found approximately 50-50 ratio of isomers in the varying solvents. To explain this he postulated a two point adsorption on the catalyst (46).



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This would then lead to some equatorial alcohol. Balasubramian and Padma (1968) also found in the hydrogenation of 1-methyl-2,6-diphenyl-4-piperidone they obtained a greater yield of the equatorial alcohol than would be expected.

Mistryukov separated and confirmed the configuration of the isomers by gas-liquid chromatography on polyethylene glycol (treated with KOH), and column chromatography using alumina (activity II) eluted with ether-CH₃OH(NH₃).

His argument for the configurational assignment is that the β -(cis)-isomer having an axial hydroxyl group which is hindered by 1,3-diaxial hydrogens and a methyl group will be less adsorbed on the column and come off first, whereas the α -(trans)-isomer, having an equatorial hydroxyl group which is less hindered will be adsorbed more strongly to the

column and come off last (Barton, 1953, Ungnade, 1948, and Weinstein, 1955).

Some physical characteristics were given: α -(trans)-1,3-dimethyl-4-piperidinol hydrochloride had a m.p. of 183-184°C and the base had a m.p. of 43-44°C. The β -(cis)-isomer was described as a thick colorless oil, no boiling point was given, nor was a melting point of a derivative given. Ganellin and Speckett (1965) also synthesized the alcohol by the reduction of the ketone with aluminium isopropoxide. They did not attempt to separate the isomers, and they found the racemic alcohol had a b.p. of 64°C at 0.25 mm, and the picrate had a m.p. of 183-184°C.

C. Procedure Adopted in Thesis

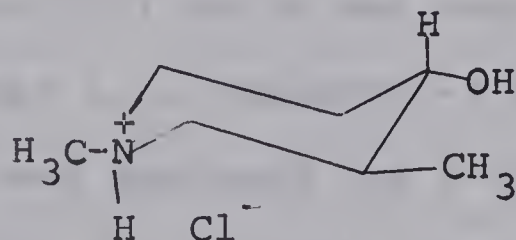
Mistryukov (1965) reduction procedures show varying degrees of stereospecificity; e.g. lithium aluminium hydride gives α -(trans) as the major component; and aluminium isopropoxide gives β -(cis) as the major component, and Adams catalyst gives a 50-50 mixture. The above reduction procedures were investigated in order to isolate the two isomers and investigate their purification by fractional crystallization of solid derivatives rather than by the use of column chromatography.

1. Lithium Aluminium Hydride

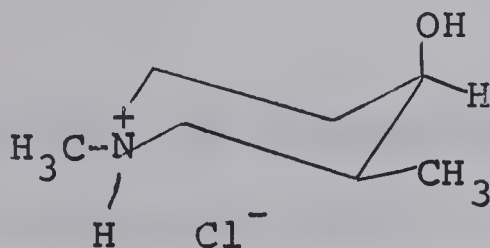
This reduction procedure, as stated by Mistryukov (1965) yields 64% of the trans isomer and 36% of the cis isomer. The reduction procedure adopted was similar to that

of Mistryukov. The ketone was added drop by drop to an ethereal solution of lithium aluminium hydride just fast enough to keep the solution refluxing. Refluxing was continued for a further eight hours, and then the reaction mixture was decomposed with ice water. The ether layer was dried and evaporated to yield 91% of the isomeric alcohols. The infrared spectrum confirmed complete reduction. The base was distilled at 1 mm and had a b.p. of 78°C; two fractions were not obtained and thus fractional distillation would not be a good method for the separation of the isomers.

Initially it was decided to try to separate the isomers as the hydrochloride salts. The base was dissolved in absolute alcohol and dry hydrogen chloride gas was passed through the solution until acidic; anhydrous ether was then added drop by drop to the cloud point and the solution was then allowed to crystallize at room temperature. A fraction of crystals was obtained after 24 hours, which had a m.p. of 184-186°C, which was about 60% of the total yield. The melting point did not change after several recrystallizations. This fraction was therefore identified as the α -(trans)-isomer (47), because of the correlation of the melting point with that of Mistryukov (1965) and PMR evidence which will be given later.



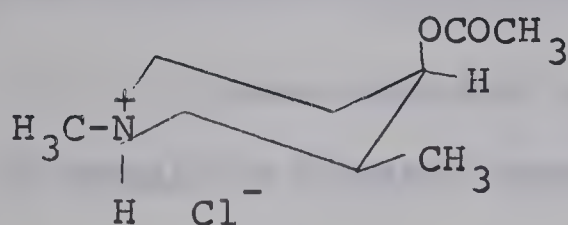
The mother liquor was then placed in the refrigerator and after one week, no other fraction of crystals was obtained (it was subsequently found that the pure β -(cis)-hydrochloride (48) was very difficult to crystallize due to it being slightly hygroscopic).



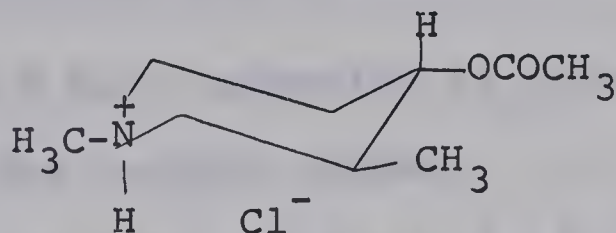
48

Due to the difficulty in crystallizing the β -hydrochloride, the free base was liberated from the mother liquor and acetylated with acetyl chloride in ethyl acetate in the hope that the acetate hydrochloride could be crystallized out of solution. After eight hours of refluxing, no solid had precipitated out. The reaction mixture was then cooled and placed in the refrigerator, and after 48 hours a solid was obtained.

The acetoxy ester (64) which precipitated out was slightly hygroscopic and had a distinctly different melting point (145-146°C) from that of the α -acetoxy ester hydrochloride (58) (208-210°C) which was made for comparison from the already separated α -1,3-dimethyl-4-piperidinol. This acetoxy ester (64) was assigned the β -(cis)-configuration, and the purity of the two isomeric esters was confirmed from their PMR spectra which will be discussed later.



64



58

The β -acetoxy ester was reduced back to the free alcohol with lithium aluminium hydride. The hydrochloride salt (48) was then made in the usual manner. Crystallization occurred in two weeks from alcohol-ether. The melting point was taken in a sealed tube due to the compound being hygroscopic, and was found to be 112-113°C, which was quite different from the α -hydrochloride.

It was interesting to note that when the α -(trans)-acetoxy ester was made by the same procedure as the β -(cis)-ester it crystallized out during the reaction, while the β -acetoxy ester hydrochloride did not crystallize out until the reaction mixture was cooled. Subsequently we acetylated the total crude reduction product, to see if one isomer would crystallize out during the reaction and if the other isomer would crystallize out of the mother liquors. This was found to be true and the purity was confirmed by the PMR spectra of the products. The pure alcohols were obtained by the reduction of the acetoxy ester with lithium aluminium hydride. This procedure was adopted as the standard practice for obtaining the pure cis and trans alcohols. The percentage yield of each isomer will be discussed later.

2. Meerwein Ponderf Veerly Reduction (M.P.V. Reduction)

It was decided to try the M.P.V. reduction in order to obtain a greater quantity of the β -(cis)-isomer. Mistryukov (1965) states that he obtains a 64% yield of the axial alcohol and 36% of the equatorial alcohol. The procedure he used was as follows: equimolar portions of the ketone and aluminium isopropoxide in 75 ml of isopropanol were refluxed for 3.5 hours and decomposed with 25 ml of 50% NaOH. The organic layer was separated, acidified to congo red and evaporated to dryness. The base was isolated by the addition of solid NaOH and extraction with ether. The above method was not adopted, but we proceeded as follows: equimolar portions of the ketone and aluminium isopropoxide were dissolved in 75 ml of isopropanol, the flask was connected to a vigreux column and the acetone was distilled off. The reaction was deemed complete when the distillate gave a negative test for acetone; this occurred after nine hours. The reaction mixture was decomposed with 50% sodium hydroxide and the basic alcohol was extracted with ether. The total crude reduction product was acetylated in the usual manner with acetyl chloride and ethyl acetate. After eight hours refluxing a solid had precipitated and this was identified as the α -isomer. From the mother liquor, after cooling, the β -isomer was obtained. The pure alcohols were obtained by reduction of the acetoxy ester with lithium aluminium hydride.

3. Adams Catalyst

In the hydrogenation of ketones over platinum catalyst, the main product would be expected to be the axial (cis) alcohol (Weckler, 1956). It was decided to try this reduction because Mistryukov (1965a) obtained a 55/45 mixture of equatorial to axial alcohol isomers which was unexpected. The reduction was carried out using 10% platinum oxide in absolute alcohol at room temperature and atmospheric pressure. The isomers were separated as before, and we obtained only the axial (cis) isomer.

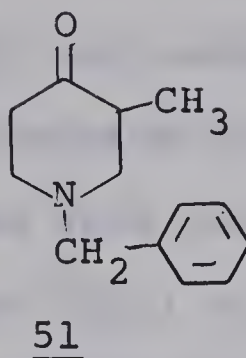
4. Palladium Charcoal

In the literature we found that no reductions of piperidones had been done using palladium charcoal at room temperature and atmospheric pressure. After five days no hydrogen had been taken up and the ketone was recovered unchanged. Therefore, palladium does not serve as a catalyst in this reduction.

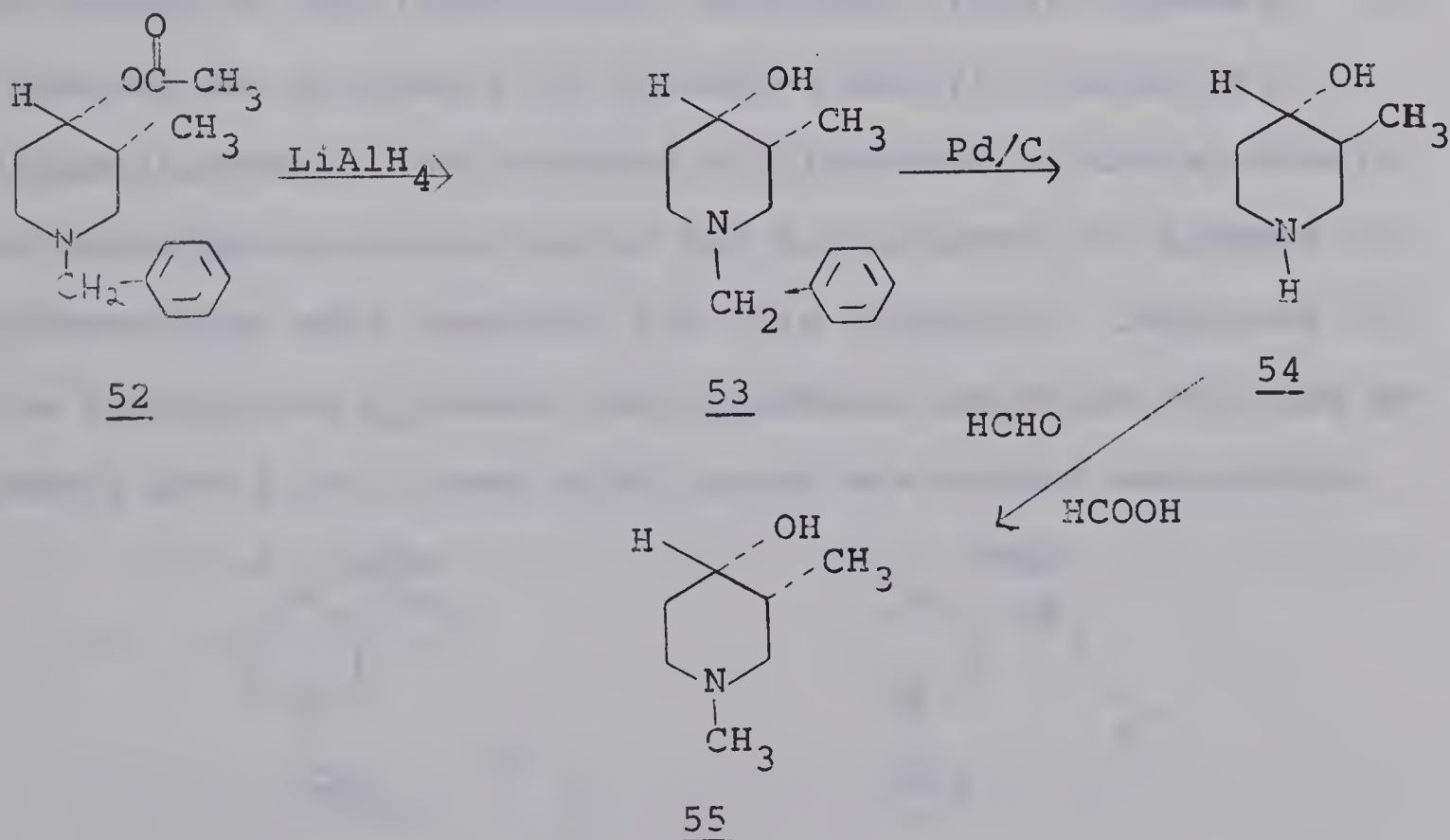
The analysis of the isomeric mixtures will be discussed later.

5. From N-Benzyl-3-Methyl-4-Piperidone

Due to the initial problem of obtaining the β -(cis)-1,3 -dimethyl-4-piperidinol, it was decided to try to obtain the β -isomer from N-benzyl-3-methyl-4-piperidone (51). The ketone was reduced with lithium aluminium hydride in the usual manner, and from the PMR spectra (explained later)



of the total crude reduction product, both isomers could be identified. Attempts were made to form a hydrochloride salt, but these failed. The isomers were eventually fractionally crystallized as their acetoxy ester hydrochlorides (Casy and Hassan, 1970), α -(trans)-isomer m.p. 255-256°C, β -(cis)-isomer m.p. 180-182°C, and their purity was determined by their PMR spectra. The procedure used for obtaining the pure β -(cis)-1,3-dimethyl-4-piperidinol is given below (Scheme III).



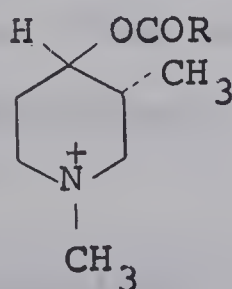
Scheme III

Synthesis of β -1,3-Dimethyl-4-Piperidinol
from N-Benzyl-3-Methyl-4-Piperidone

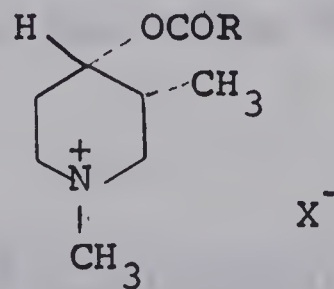
The acetoxy ester (52) was reduced back to the pure alcohol (53) with lithium aluminium hydride in ether. The alcohol was then debenzylated with palladium charcoal in ethanol to yield N-H compound (54); this was then methylated with formic acid and formaldehyde to yield the desired compound β -1,3 -dimethyl-4-piperidinol (55). The hydrochloride was then made and the melting point was identical with that of β -1,3 -dimethyl-4-piperidinol hydrochloride obtained by the original procedure.

IV SYNTHESIS OF ESTERS OF ISOMERIC 1,3-DIMETHYL-4-PIPERIDINOLS

No atropine analogs (58-69) of type (56) and (57) could be traced in the literature. Biniecki (1969), however, reported the synthesis of 1-butyl-3-methyl-4-piperidyl-diphenylacetate. He reported difficulties in the synthesis of the diphenylacetate as we had encountered; no isomers or pharmacology were reported for this compound. Compounds of the type (56) and (57) where the 4-methine proton is replaced by phenyl and R is a lower alkyl group are potent analgesics.



56



57

<u>R</u>	<u>X</u>	<u>No.</u>	<u>R</u>	<u>X</u>	<u>No.</u>
CH ₃	HCl	<u>58</u>	CH ₃	HCl	<u>64</u>
CH ₃	CH ₃ I	<u>59</u>	CH ₃	CH ₃ I	<u>65</u>
(C ₆ H ₅) ₂ CH	HCl	<u>60</u>	(C ₆ H ₅) ₂ CH	HCl	<u>66</u>
(C ₆ H ₅) ₂ CH	CH ₃ I	<u>61</u>	(C ₆ H ₅) ₂ CH	CH ₃ I	<u>67</u>
(C ₆ H ₅) ₂ COH	HCl	<u>62</u>	(C ₆ H ₅) ₂ COH	HCl	<u>68</u>
(C ₆ H ₅) ₂ COH	CH ₃ I	<u>63</u>	(C ₆ H ₅) ₂ COH	CH ₃ I	<u>69</u>

The acetate hydrochlorides (58) and (64) were synthesized by the same procedure as compounds (14) and (20), in excellent yields. The diphenylacetate hydrochlorides (60) and (66) were synthesized by the acid chloride method and the transesterification method, in yields between 20 and 40%. The benzilates (62) and (68) were synthesized again by the transesterification procedure, in yields of 30-60%. All methiodides were made by the usual procedure, in yields greater than 85%.

All the α -ester hydrochlorides were stable, the β -esters were slightly hygroscopic and all the methiodides were stable. The isomeric purity of the esters was checked by PMR spectroscopy.

V STEREOCHEMISTRY OF THE ISOMER OF 1,3-DIMETHYL-4-PIPERIDINOL

The Russian evidence as stated earlier is suggestive of their stereochemistry, but not conclusive. PMR evidence

has been obtained for both their conformation and their configuration.

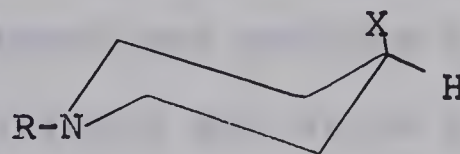
A. 4-Methine Signal

Principle

Stereochemical information about piperidinol derivatives of the type (70a) and (70b) may be obtained from the PMR characteristics of the 4-methine proton. In the first



70a

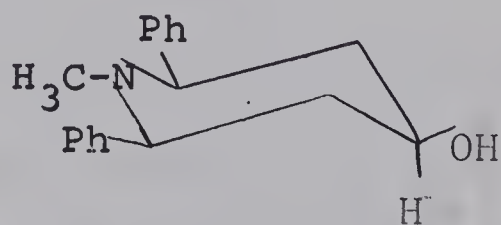


70b

case, the signal of the axial proton in (70a) is generally at higher field than that of the equatorial proton in (70b) as a result of long range deshielding effects associated with carbon-carbon single bonds that bear a 2,3 relationship to the proton in question (Jackman, 1959; ApSimon et al., 1967). Secondly, the equatorial signal will show less extensive spin-spin coupling with vicinal neighbours than the axial signal as a result of the dihedral angle (ϕ) dependence of coupling constants (Karplus, 1959, 1960). In (70a) two axial-axial ($\phi = 180$) and two axial-equatorial ($\phi = 60$) coupling will operate, whereas in (70b) two axial-equatorial ($\phi = 60$) and two equatorial-equatorial ($\phi = 60$) coupling^s will operate. In cyclohexane rings J_{aa} usually falls in the range 8-14 Hz, whereas J_{ae} and J_{ee} coupling have

significantly smaller values in the range 0-6 Hz (Thomas, 1968). As a result the axial methine signal will be broader than the equatorial resonance and if resolved, will display typical J_{aa} and J_{ae} coupling constants. Methine signals often may not be clearly resolved, and in such cases, features of value are the signal base width or width at half height (W_h). Long range coupling constants also contribute to signal width so absolute values may be deceptive. Comparative values of signal width between the methine signals of isomers may, however, be significant and allow their differentiation.

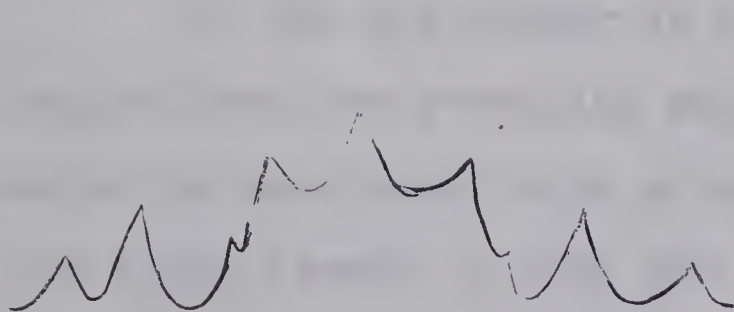
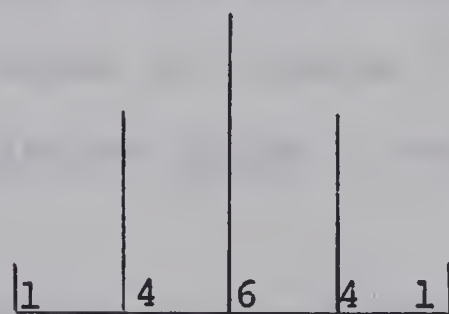
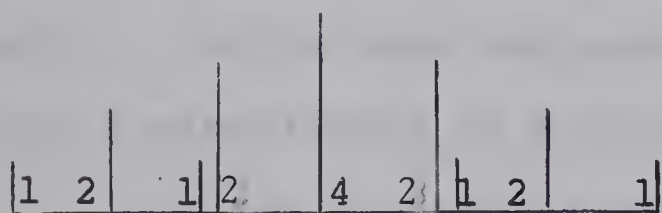
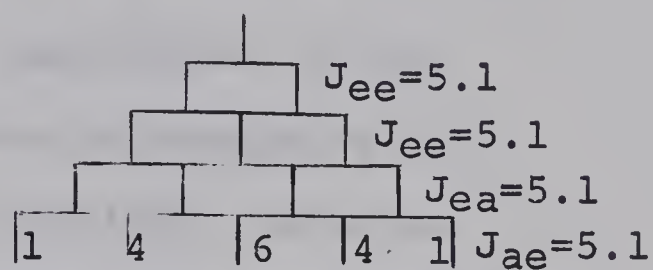
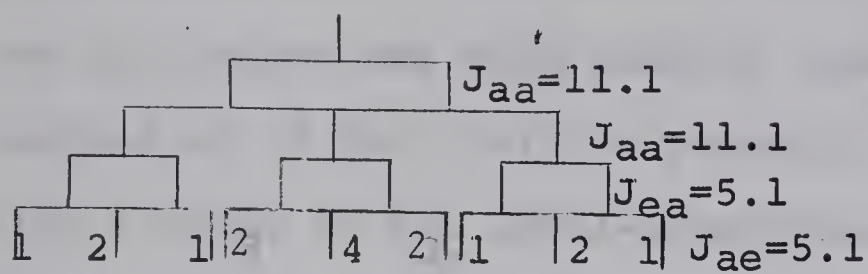
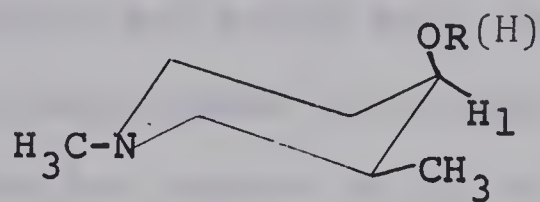
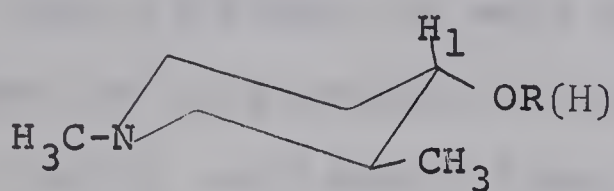
The form and dimensions of the 4-methine signal to be anticipated if the 4-proton adopts a preferred axial or equatorial conformation may be gauged from data upon β -1-methyl-2,6 - diphenyl-4-piperidinol (71) (Chen and LeFevre, 1965b) a compound fixed in the chair conformation by the



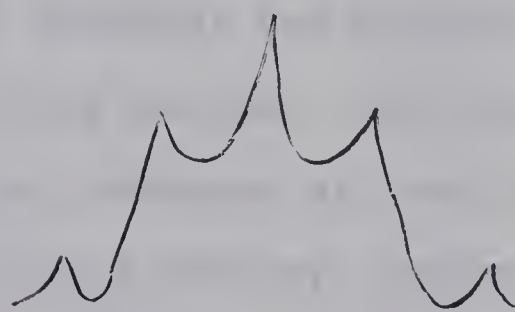
71

bulky 2,6 -diphenyl substituents. The 4-methine PMR signal of this piperidinol appears as a nonet from which the two coupling constants J 5.1 and J 11.1 may be derived by 1st order treatment. Taking the former value as the J_{ae} and the J_{ee} value and the latter as the J_{aa} (to a first-approximation) signals due to axial and equatorial 4-methine

protons may be constructed as shown in Figure 1.



Width 33 Hz



Width 20 Hz

Figure 1 Calculated PMR Spectrum of the 4-methine proton in the isomeric 1,3-dimethyl-4-piperidinols

As can be seen from table VI the 4-methine signal in the *cis*-isomer is well resolved and moved well down field from the ring protons; in the *trans*-isomer the signal can be fairly confidently identified but cannot be so well resolved because its higher field side overlaps the main ring proton band. The actual width of the proton signal in the *cis*-isomer was much smaller than calculated (16 Hz instead of 20 Hz); this is probably due to assigning too high a value to the axial-equatorial coupling. Also as was expected, the axial proton is higher field and broader than the equatorial proton. This is shown in Figures 2 and 3, which show the spectrum of cis- and trans-1,3-dimethyl-4-piperidinol in pyridine.

In the N-benzyl-3-methyl-4-piperidinol, the 4-methine proton can be seen readily in both isomers in CDCl_3 . The N-benzyl group therefore must have a long-range deshielding effect on the 4-methine proton.

In the cis-isomer in both the N-methyl and N-benzyl derivatives the 4-methine proton is very narrow, 16-18 Hz, which is consistent with an equatorial hydrogen at the C-4; the trans-isomer in both the N-methyl and N-benzyl derivatives has a wide 4-methine signal (31-32 Hz), and this is consistent with an axial hydrogen. The chemical shifts of the 4-methine signals (trans higher than cis) as previously explained, is further proof of the configuration of the molecule.

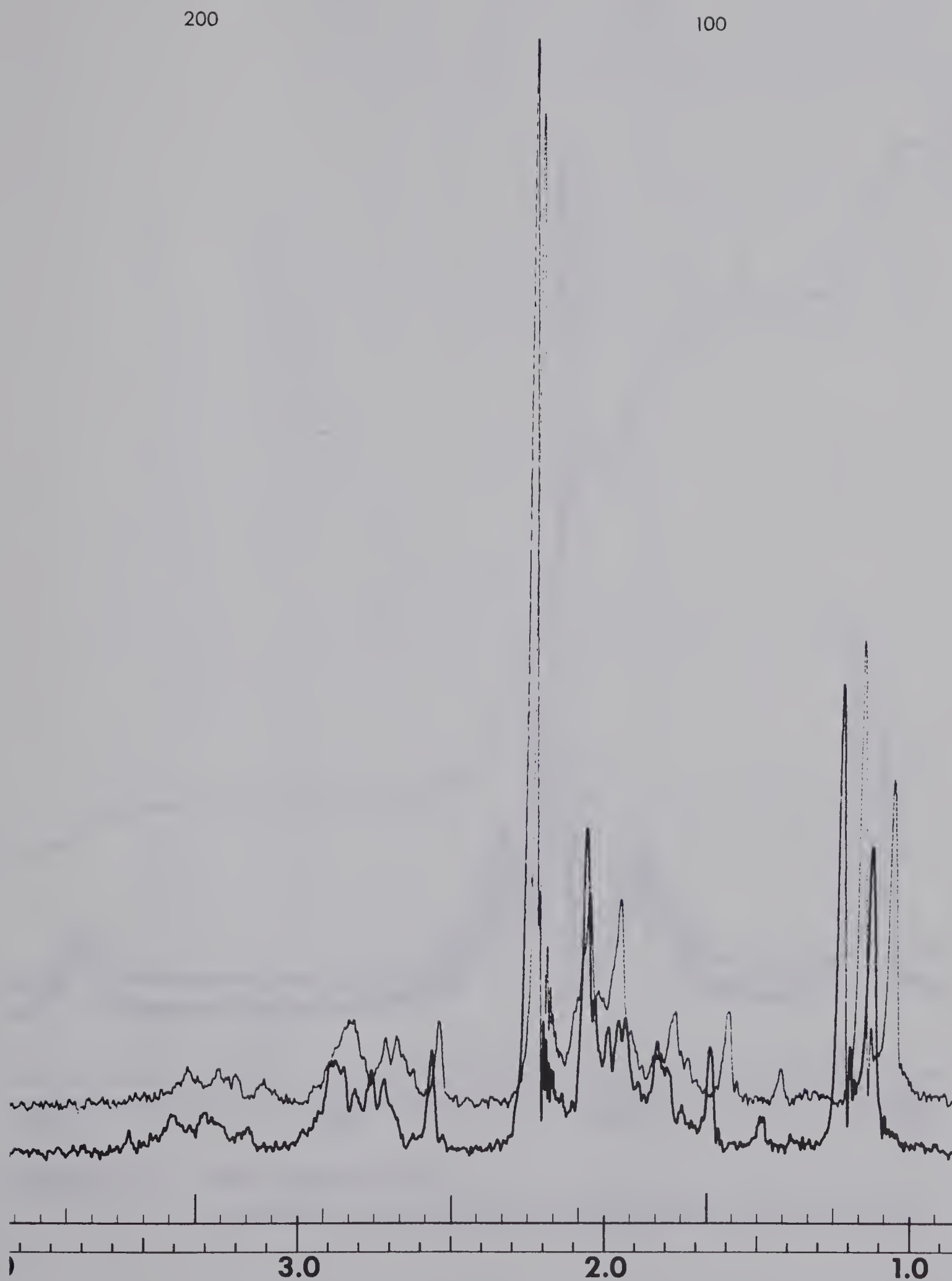


Figure 2. PMR Spectrum of
 α -(trans)-1,3-dimethyl-4-piperidinol in pyridine

200

100

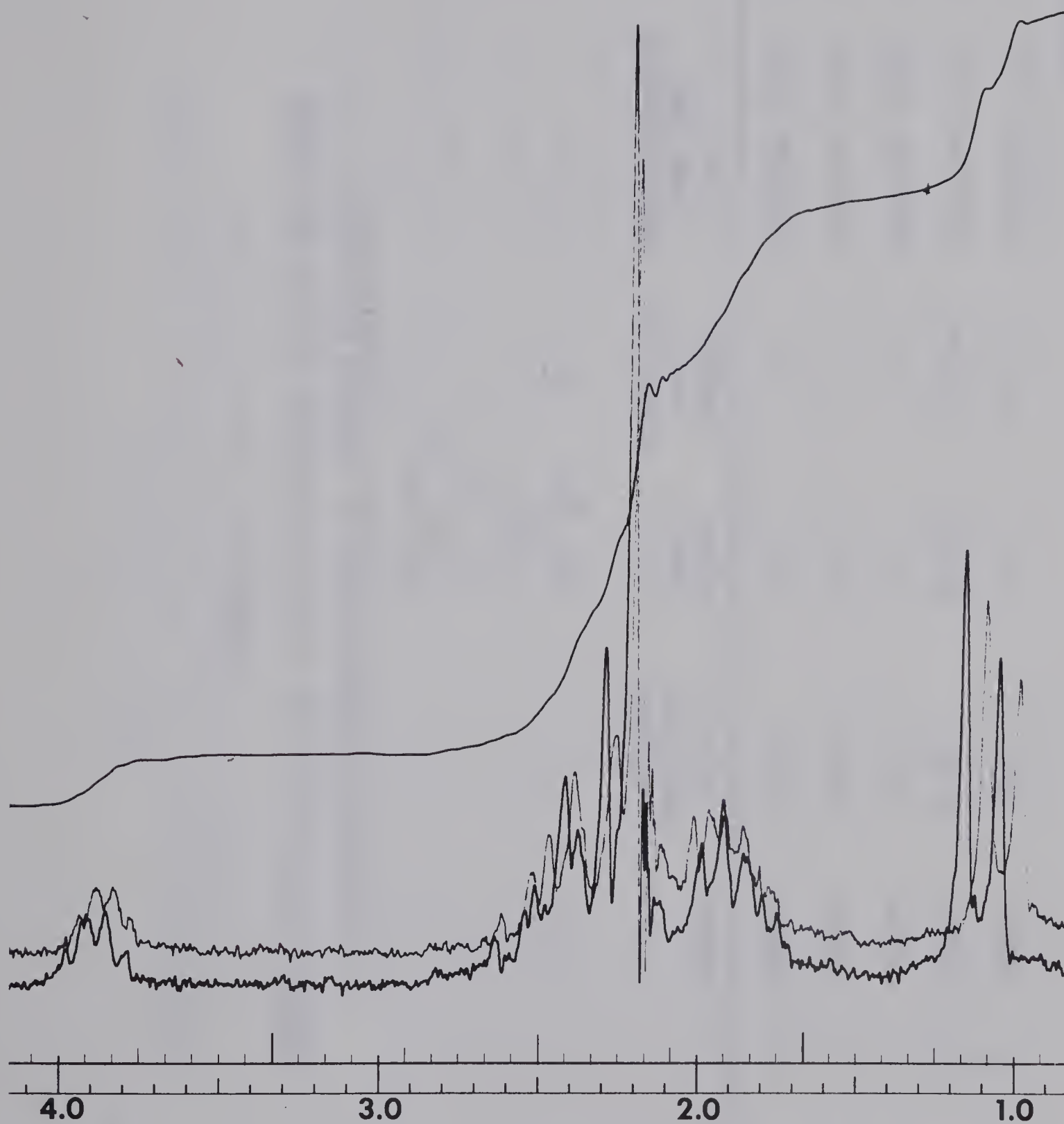
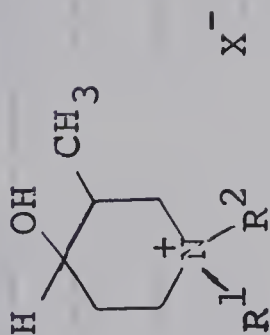


Figure 3. PMR Spectrum of
 β -(cis)-1,3-dimethyl-4-piperidinol in pyridine

TABLE VI
CHARACTERISTICS OF THE 4-METHINE PROTON IN CIS AND TRANS
1,3-DIMETHYL-4-PIPERIDINOL IN VARYING SOLVENTS



R^1	R^2	X	Isomer	Position from TMS in δ	Base width	Width at half height	N-Me Position from TMS in δ	Solvent
CH ₃	--	--	trans	(a)	--	--	singlet 2.15	CCl ₄
CH ₃	--	--	trans	(a)	--	--	singlet 2.20	CDCl ₃
CH ₃	--	--	trans	(b)	--	--	singlet 2.06	Benzene
CH ₃	--	--	trans	3.25	31 Hz	17 Hz	singlet 2.13	Pyridine
CH ₃	--	--	trans	(a)	--	--	singlet 2.10	DMSO-D ₆

continued

TABLE VI (continued)

CHARACTERISTICS OF THE 4-METHINE PROTON IN CIS AND TRANS

1,3-DIMETHYL-4-PIPERIDINOL IN VARYING SOLVENTS

R ¹	R ²	X	Isomer	Position from TMS in δ	Base width	Width at half height	N-Me Position from TMS in δ	Solvent
CH ₃	H	Cl	trans	(a)	--	--	singlet 2.65	DMSO-D ₆
CH ₃	CH ₃	I	trans	(a)	--	--	singlet 3.15	D ₂ O
CH ₃	CH ₃	I	trans	(a)	--	--	Doublet 3.0 - 2.95	DMSO-D ₆ (c)
CH ₃	--	--	cis	3.48	(b)	--	singlet 2.08	CCl ₄
CH ₃	--	--	cis	3.73	16 Hz	7.5 Hz	singlet 2.25	CDCl ₃
CH ₃	--	--	cis	3.68	(b)	--	singlet 2.11	Benzene
CH ₃	--	--	cis	3.86	18 Hz	8.5 Hz	singlet 2.18	Pyridine
CH ₃	--	--	cis	3.48	16 Hz	7.5 Hz	singlet 2.08	DMSO-D ₆
CH ₃	H	Cl	cis	3.50	16 Hz	7.5 Hz	singlet 2.15	DMSO-D ₆
CH ₃	CH ₃	I	cis	3.65	16 Hz	8.0 Hz	Doublet 3.15 - 3.10	DMSO-D ₆ (c)

continued

TABLE VI (continued)

CHARACTERISTICS OF THE 4-METHINE PROTON IN CIS AND TRANS

1,3-DIMETHYL-4-PIPERIDINOL IN VARYING SOLVENTS

R^1	R^2	X	Isomer	Position from TMS in δ	Base width	Width at half height	N-Me Position from TMS in δ	Solvent
$CH_2-C_6H_5$	--	--	cis	3.70	17.0 Hz	8.5 Hz	--	$CDCl_3$
$CH_2-C_6H_5$	--	--	trans	3.10	32.0 Hz	16.5 Hz	--	$CDCl_3$

- (a) - not resolved, lost in ring proton signal.
- (b) - moved down slightly, can see some of it.
- (c) - OH split -- explanation later.

B. Acylation Shift

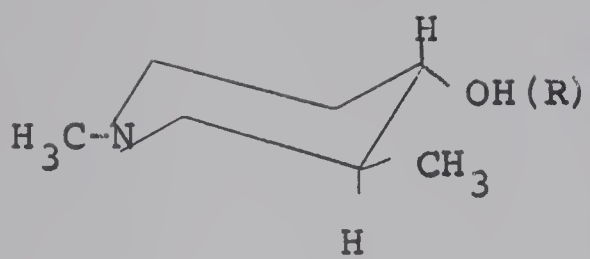
Due to the fact that in the trans-isomer the 4-methine proton cannot be clearly resolved, the acylation shift was investigated in the hope that it would lead to spectral improvements.

Principle

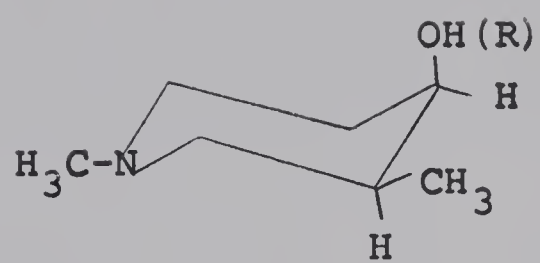
When an alcohol is esterified, this increases the electronegativity around the α -hydrogen and a subsequent paramagnetic shift is produced. With primary alcohols this is approximately 0.50 ppm. Acylation of secondary alcohols causes the α -proton to move by 1.0-1.5 ppm to lower field ~~ness~~ (Culvenor, 1966). Thus the assignment of a band in the 5-7 δ region of the spectrum of an alcohol to a proton α to a hydroxyl group is confirmed if the band moves to lower field in the acyl derivative (Jackman, 1959).

In the acetoxy ester of α -(trans)-1,3-dimethyl-4-piperidinol the 4-methine proton is shifted down field away from the main ring proton band (Figure 4) and the same is true for the cis-isomer (Figure 5).

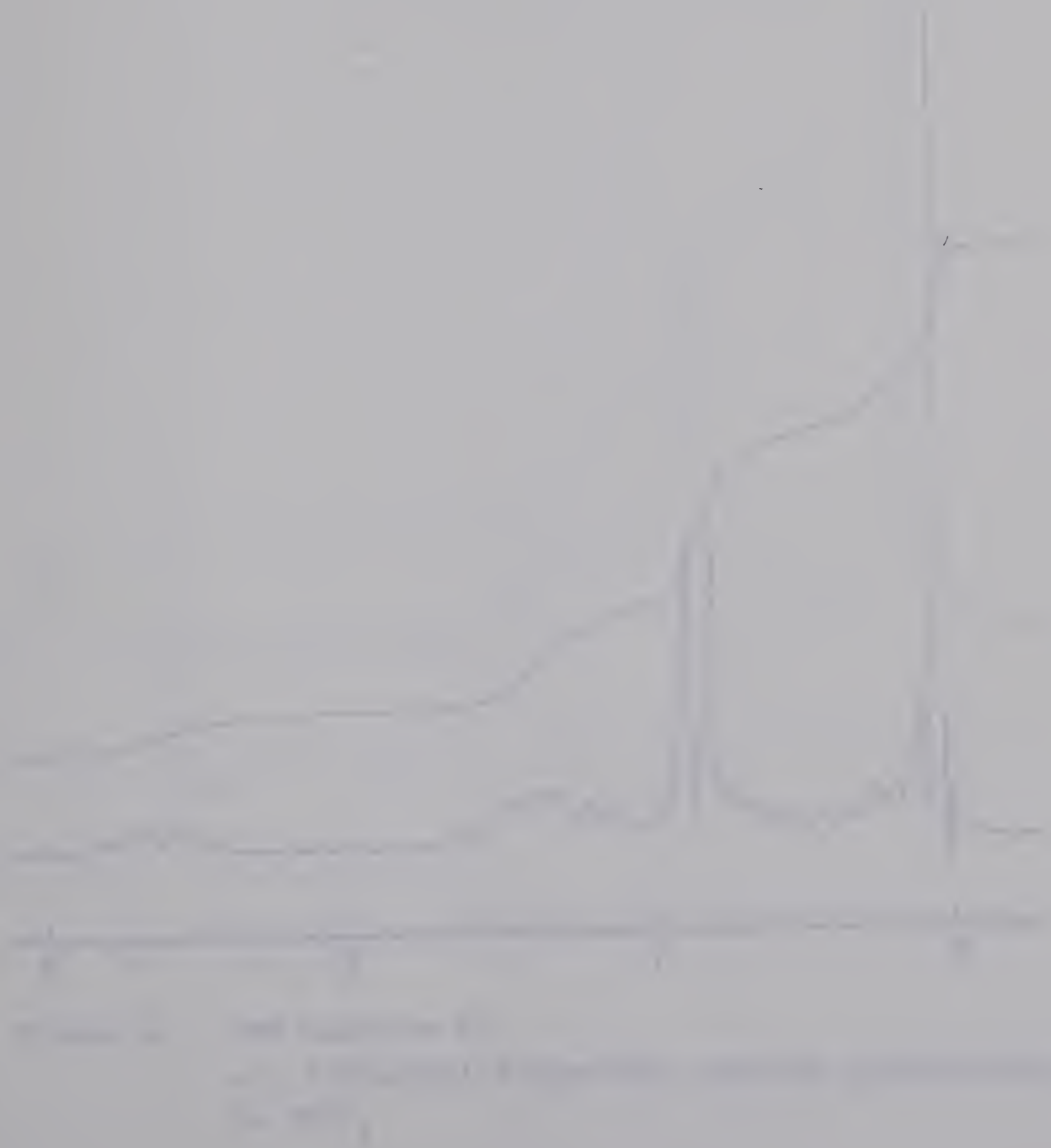
From Table VII it can be seen that in the ester derivatives of the trans-isomer, the 4-methine signal is very broad (32 Hz) and occurs at a higher field (approximately 20 Hz) than the corresponding cis signal which has a narrow (16 Hz) 4-methine signal. The signal widths and their position are good evidence of the configuration and conformation of the α - and β -1,3-dimethyl-4-piperidinol to be (72) and (73) which are respectively the trans- and cis-isomer.



72



73



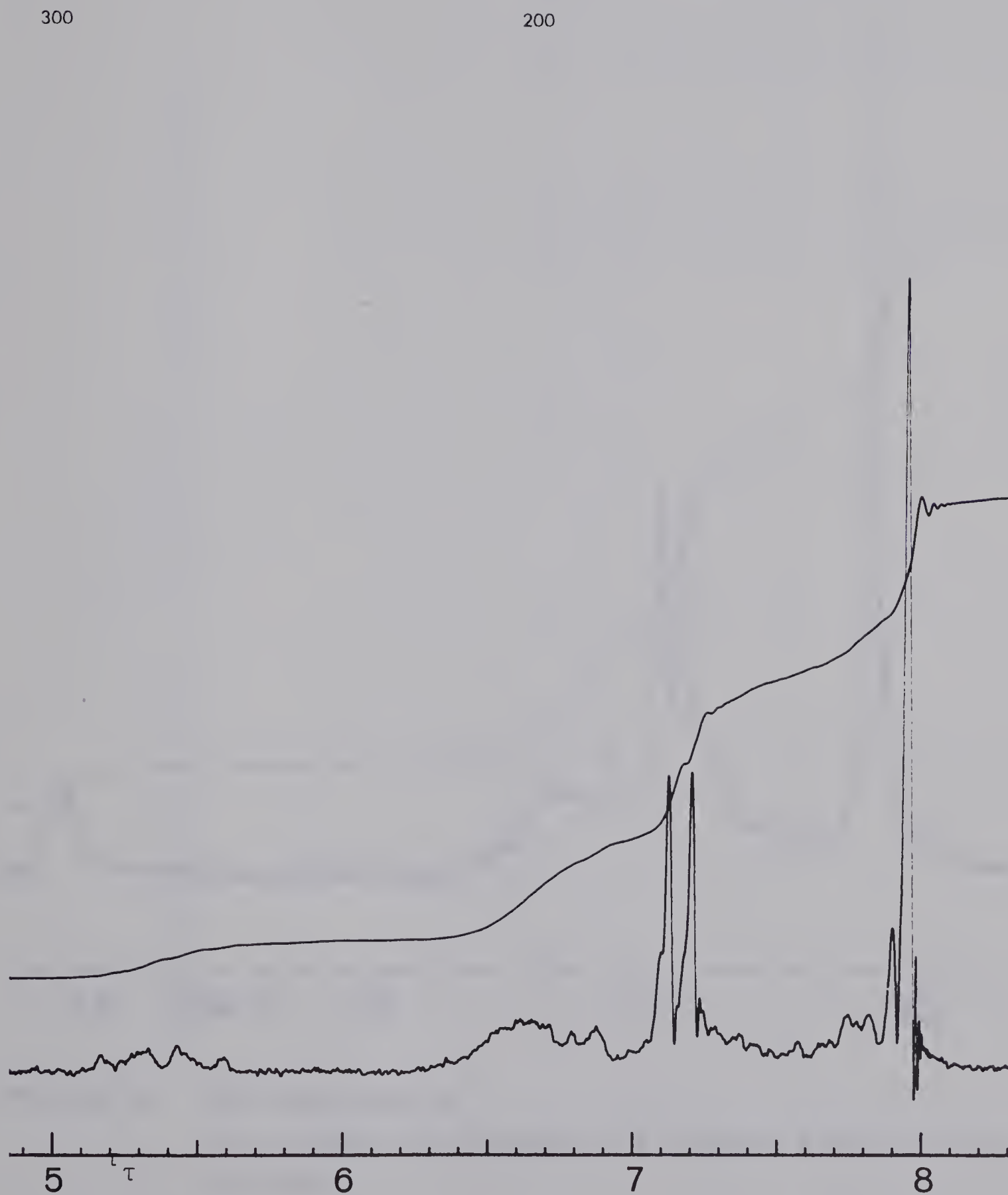


Figure 4. PMR Spectrum of
 α -1,3-dimethyl-4-piperidyl acetate hydrochloride
in CDCl_3

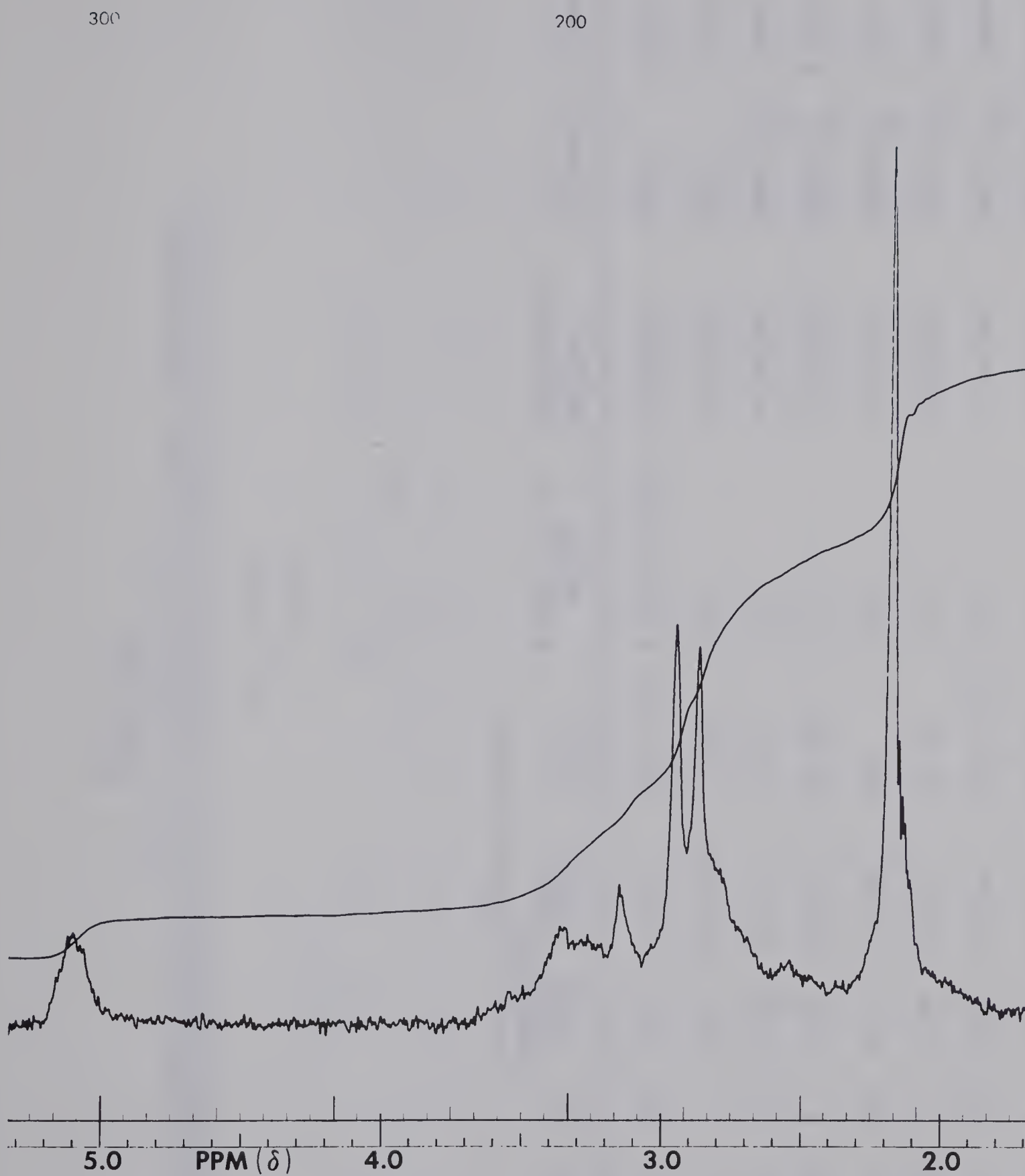
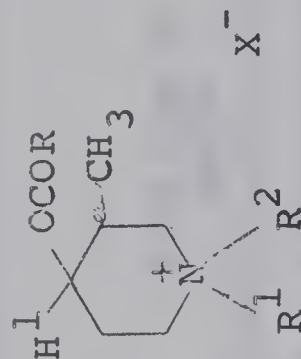


Figure 5. PMR Spectrum of
 β -1,3-dimethyl-4-piperidyl acetate hydrochloride
in CDCl_3

TABLE VII

PMR CHARACTERISTICS OF 1,3 -DIMETHYL-4-PIPERIDYL DERIVATIVES



R	R ¹	R ²	X	Position from TMS		H ¹ (W _h)	Position of NR ¹ R ²	Characteristics	Solvent	Isomer
				Base	Width					
CH ₃	CH ₃	H	Cl	4.65	32 Hz	16.5 Hz	2.88-2.81(a)	doublet	CDCl ₃	trans
CH ₃	CH ₃	-	-	4.40	31.5 Hz	17 Hz	2.06	singlet	CDCl ₃	trans
CH ₃	CH ₃	H	Cl	4.56	32 Hz	16 Hz	2.68	singlet	DMSO-D ₆	trans
CH ₃	CH ₃	CH ₃	I	4.61	34 Hz	16 Hz	3.13	singlet	DMSO-D ₆	trans
(C ₆ H ₅) ₂ CH	CH ₃	H	Cl	4.68	31 Hz	(b)	2.66	singlet	DMSO-D ₆	trans
(C ₆ H ₅) ₂ CH	CH ₃	CH ₃	I	4.70	32 Hz	16 Hz	3.13	singlet	DMSO-D ₆	trans
(C ₆ H ₅) ₂ COH	CH ₃	H	Cl	4.66	31 Hz	16.5 Hz	2.61	singlet	DMSO-D ₆	trans
(C ₆ H ₅) ₂ COH	CH ₃	CH ₃	I	4.68	31 Hz	16 Hz	3.11	singlet	DMSO-D ₆	trans

continued

TABLE VII (continued)

PMR CHARACTERISTICS OF 1,3 -DIMETHYL-4-PIPERIDYL DERIVATIVES

R	R ¹	R ²	X	Position from TMS		(W _h)	Position of NR ¹ R ²	Characteristics	Solvent	Isomer
				TMS	Base Width					
CH ₃	CH ₃	H	Cl	5.03	16 Hz	7.0 Hz	2.90-2.81(a)	doublet	CDCl ₃	cis
CH ₃	CH ₃	-	-	4.93	17 Hz	6.5 Hz	2.26	singlet	CDCl ₃	cis
CH ₃	CH ₃	H	Cl	4.93	17 Hz	8.0 Hz	2.71	singlet	DMSO-D ₆	cis
CH ₃	CH ₃	CH ₃	I	4.85	13 Hz	6.0 Hz	3.23-3.16	doublet	DMSO-D ₆	cis
(C ₆ H ₅) ₂ CH	CH ₃	H	Cl	5.03	(c)	(c)	2.63-2.56(a)	doublet	CDCl ₃	cis
(C ₆ H ₅) ₂ CH	CH ₃	H	Cl	5.0	13 Hz	7.0 Hz	2.76	singlet	DMSO-D ₆	cis
(C ₆ H ₅) ₂ COH	CH ₃	CH ₃	I	4.95	13.5 Hz	6.0 Hz	2.61	singlet	DMSO-D ₆	cis
(C ₆ H ₅) ₂ COH	CH ₃	H	Cl	5.03	13.0 Hz	6.0 Hz	2.73	singlet	DMSO-D ₆	cis
(C ₆ H ₅) ₂ COH	CH ₃	CH ₃	I	5.01	15.0 Hz	6.0 Hz	3.13-3.08	doublet	DMSO-D ₆	cis

continued

C. Hydroxyl Coupling

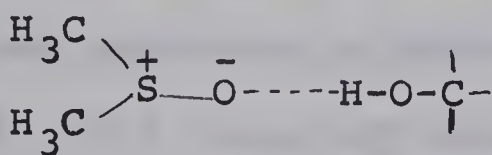
Principle

The PMR spectra of an alcohol usually shows the hydroxyl proton as a sharp peak between $\delta 0.5-5.0$. The resonance frequency of the hydroxyl proton is very sensitive to temperature, concentration and solvent type due to the participation of the hydroxyl group in hydrogen bonding equilibrium. The temperature dependence of the resonance frequency of alcohols can be understood if there are alternative molecular states, e.g., associated and unassociated states, whose energy of separation is of the order K_t . Since changes in temperature will alter the population of the two states, the resonance frequency will be temperature dependent. For the same reason, the chemical shifts of hydroxylic protons are particularly sensitive to concentration and solvent type. A change in concentration results in the change of intermolecular hydrogen bonding and this leads to the shift of equilibrium between associated and unassociated states.

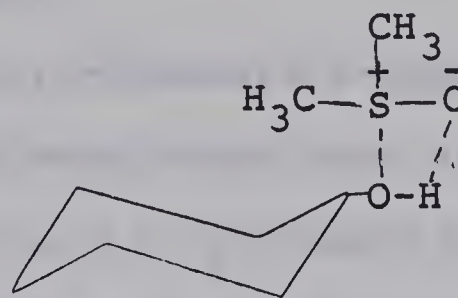
Polar solvents form strong hydrogen bonds with solute molecules and thereby afford chemical shifts of the hydroxylic proton different from those obtained in non-polar solvents. Dimethyl sulfoxide (DMSO) is one of these polar solvents. The hydroxyl proton signals of primary and secondary alcohols in DMSO- D_6 permit the detection of H-C-O-H coupling. This is attributed to strong hydrogen bonding between alcohols and the solvent, which shifts the hydroxyl proton resonance down field to about $\delta 4.0$ or lower and reduces the rate of proton

exchange sufficiently to permit observation of hydroxyl proton splitting (Chapman et al., 1964).

The hydrogen bonding of DMSO to the alcohol can be illustrated by means of the two models (74) and (75); which of the two is the more likely is undetermined.

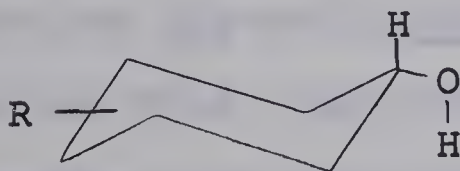


74

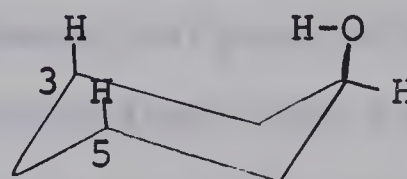


75

In isomers of type (76) and type (77), the hydroxyl resonance of type (76) would be expected to have the lower field position because the hydroxyl group has the more accessible orientation (equatorial) and should thus be more extensively hydrogen bonded to the solvent. Furthermore,



76



77

the magnitude of HCOH coupling in the equatorial isomer should be the greater because the population of axial-axial conformers ($\phi = 180$) should be higher in this isomer; in type (77) axial-axial conformers are unfavoured as a result of destabi-

lizing interaction with the 3,5-axial protons.

Rader (1966) illustrated this by using different cis/trans-isomers of 4-t-butylcyclohexanols in DMSO-D₆. He found the trans-equatorial hydroxyl signal to be more deshielded and to have a coupling constant 1.0-1.5 Hz greater than that of the axial hydroxyl signal.

In the free bases of α - and β -1,3-dimethyl-4-piperidinol the PMR spectrum in DMSO-D₆ showed a very broad band around δ 5.5. Its disappearance upon addition of D₂O identified it as the hydroxyl proton. This broadening of the hydroxyl proton and lack of resolution indicates that fairly fast proton exchange is occurring. Bass (1969) found that spectra of amino alcohols in DMSO-D₆ did not display the required coupling; he only obtained a broadening of the hydroxyl band. He found that the basicity of the amino alcohol catalyzed the rate of proton exchange, so coupling could not occur. If, however, the amino alcohol was quaternized (destroying the basic centre) coupling to the hydroxyl proton was observed.

As previously mentioned, no HCHO coupling was observed with our cis- and trans-isomers of 1,3-dimethyl-4-piperidinol; nor was this observed with N-methyl-4-piperidinol and its 3-analog. We then prepared the quaternary salts of α - and β -1,3-dimethyl-4-piperidinol, N-methyl-4-piperidinol and N-methyl-3-piperidinol, compound numbers (78), (79), (80) and (81) respectively by the usual procedure to see if coupling would be observed.

Initially the basic centres were removed by making

the hydrochloride salt of the cis (48) and trans (47) isomers, but we again did not obtain the hydroxyl coupling; presumably sufficient base (free t-amine of chloride anion) is present to catalyse the proton exchange. The spectrum of the quaternary salts did; however, show the required coupling (Table VIII).

TABLE VIII
COUPLING OF HYDROXYL PROTONS IN DMSO-D₆

Number	Compound	Position	J Value
78	α -1,3-Dimethyl-4-piperidinol Methiodide	4.96	5.0 Hz
79	β -1,3-Dimethyl-4-piperidinol Methiodide	4.93	3.5 Hz
80	N-Methyl-4-piperidinol Methiodide	4.83	4.0 Hz
81	N-Methyl-3-piperidinol Methiodide	5.30	4.0 Hz

The α -(trans)-1,3-dimethyl-4-piperidinol methiodide hydroxyl signal is slightly more down field than that of the β -(cis)-isomer and the coupling constant for the trans is slightly larger than the cis. These results confirm the configuration and conformation of the isomeric alcohols. The position of the hydroxyl proton in N-methyl-4-piperidinol methiodide (80) and its 3-analog (81) do not give any information about this configuration. Their J values do; however, indicate the hydroxyl groups of these alcohols prefer equatorial orientation.

VI ISOMERIC RATIO OF CIS-AND TRANS-1,3-DIMETHYL-4-PIPERIDINOL

It was initially tried to determine the isomeric ratio from the PMR spectra of the total products. It was hoped that the 4-methine proton signals may be isolated from one another and from other signals so separate integrations could be made, and in this way we could calculate the percentage of each isomer. However, as explained earlier, this was not possible.

The procedure used was as follows: The total crude alcohol was esterified and the isomer separated as explained earlier. The separation was quantitative, i.e. the two fractions obtained were not contaminated with one another. From the total yield of the equatorial and axial esters, it is possible to calculate the theoretical amount of the pure alcohol we would obtain if the ester was reduced back to the alcohol with lithium aluminium hydride. From the yields of the two alcohols you can calculate the percentage of each isomer.

TABLE IX

ISOMERIC RATIO OF 1,3-DIMETHYL-4-PIPERIDINOLS

Compound	Conditions	e	a
1,3-Dimethyl-4-piperidone	LiAlH_4	70	30
1,3-Dimethyl-4-piperidone	Aluminium Isopropoxide	55	45
1,3-Dimethyl-4-piperidone	PtO_2	0	100
1,3-Dimethyl-4-piperidone	PdC	0	0

The results obtained with lithium aluminium hydride correspond with that obtained by Mistryukov (1965). In the Meerwein Ponderf Veerley reduction our results are significantly different; we obtained an equatorial-axial ratio of 55 to 45, whereas Mistryukov obtained a 36 to 64 ratio. This difference can be explained.

Balasubramian and Padma (1963) explained that in reductions with aluminium isopropoxide the possibility of epimerization of the less stable alcohol to the more stable epimer, under the catalysing influence of aluminium isopropoxide should be taken into account. Mistryukov's total reaction time was 3.5 hours, and our reaction time was 9 hours. In this extra time epimerization may have occurred.

Different results using platinum oxide were also obtained. We obtained 100% of the axial alcohol, as might be expected, instead of obtaining Mistryukov's results of 69% equatorial and 31% axial. The differences stated may be due to procedures used: Mistryukov used pressure, and we used atmospheric pressure; also, the method of analysis may affect the results. In using atmospheric pressure instead of a higher pressure, the take up of hydrogen will be much slower and isomerization may be possible.

An attempt was again made to find a PMR method of analysis to confirm the above results. The total crude alcohol was acetylated using acetic anhydride this time to obtain the total crude ester instead of separating the isomers. The PMR spectra of these products showed both

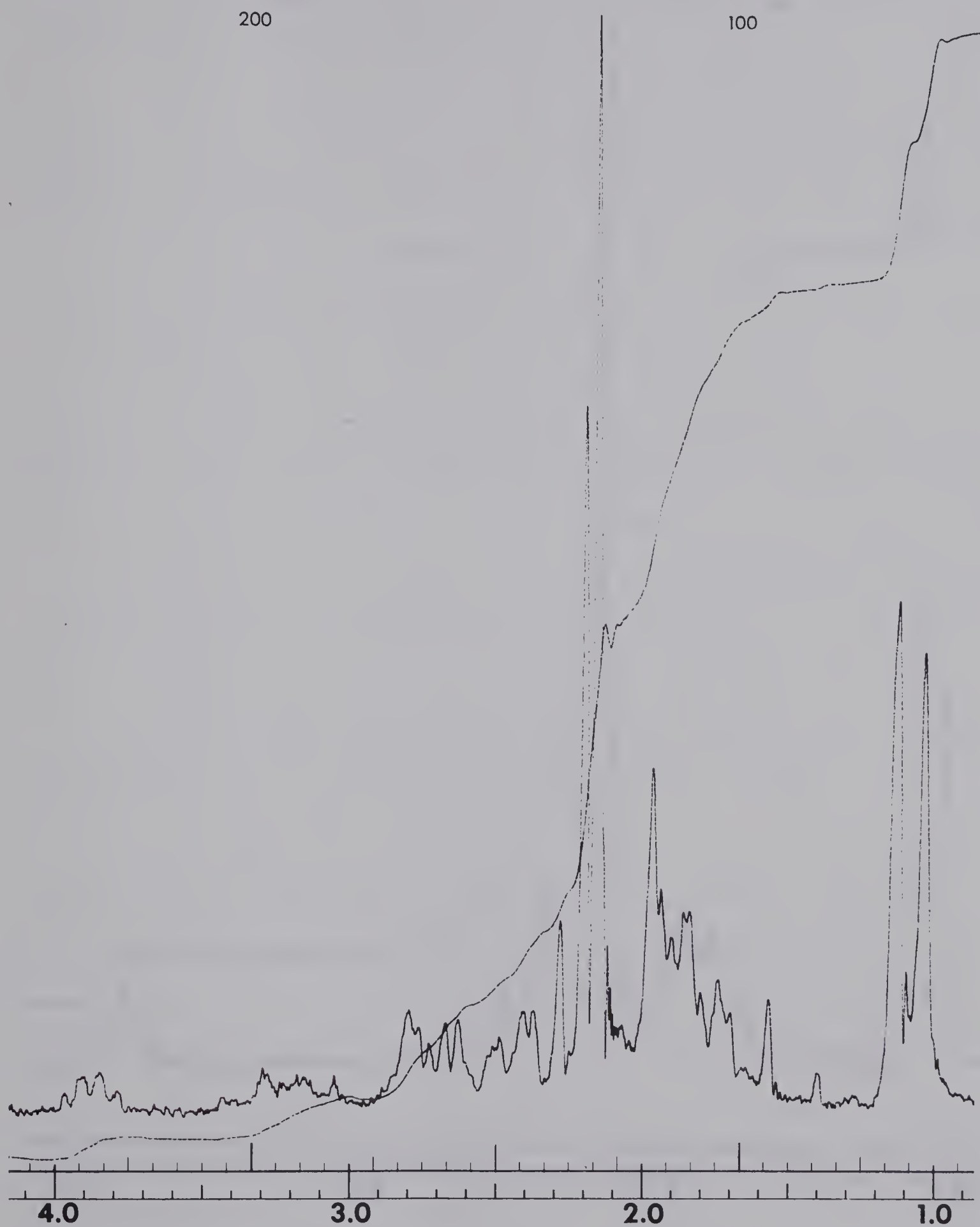


Figure 6. PMR Spectrum of total reduction products of 1,3-dimethyl-4-piperidone by lithium aluminium hydride in pyridine

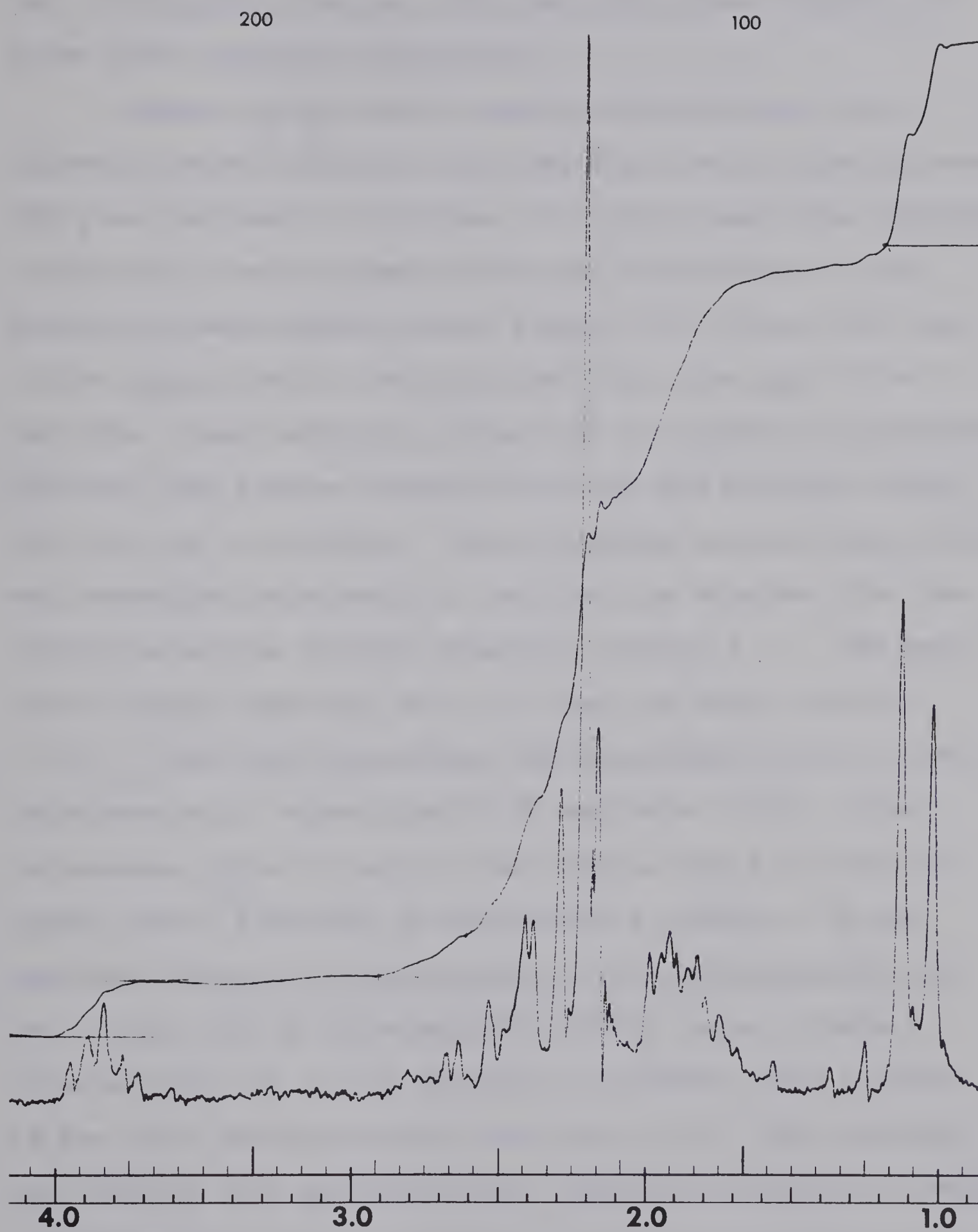


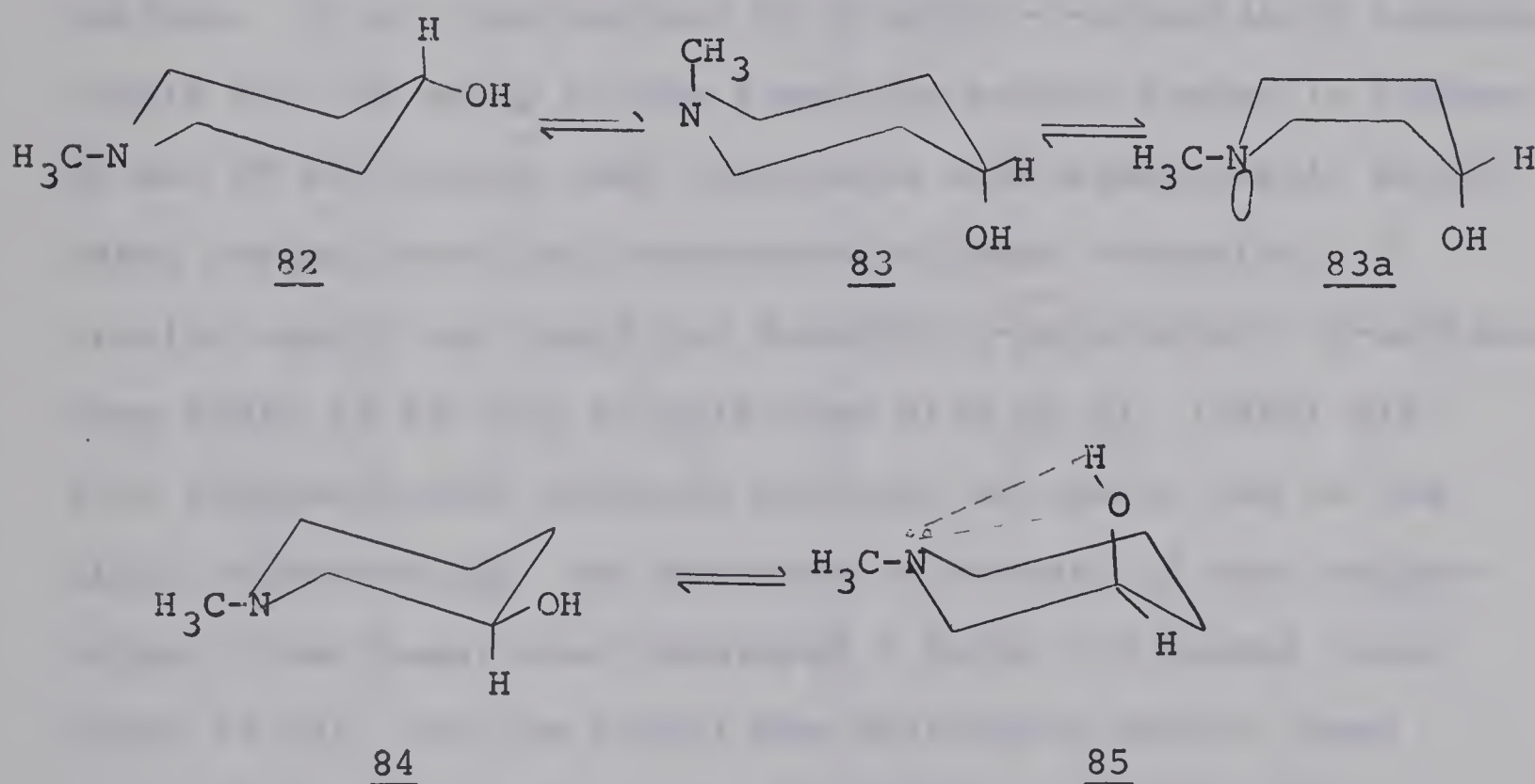
Figure 7. PMR Spectrum of the total reduction products of 1,3-dimethyl-4-piperidone by platinum oxide in pyridine

the 4-CH signals; however, they were too close together to allow their separate integration.

Demarco et al. (1968) reported that protons α to hydroxyl groups suffered large down field shifts when solvent CDCl_3 was replaced by pyridine. For this reason the spectrum of the pure α - and β -isomers were run in pyridine; it was found that each methine proton signal was visible with that of the trans-alcohol deshielded more than the cis-alcohol. The total crude reduction product of 1,3-dimethyl-4-piperidone obtained from lithium aluminium hydride and platinum oxide was then run in pyridine. Both 4-methine protons were visible and integrated separately in the spectrum obtained from the lithium aluminium hydride reduction (Figure 6). The equatorial proton resonated at δ 3.86 and the axial proton at δ 3.21. From the integration, the percentage of each isomer calculated was: equatorial 63.5% and axial 36.5%. This corresponds quite closely to our results based on yield of esters and is identical to Mistryukov's results. In the spectrum obtained in the reduction with platinum oxide, the 4-CH signal due to the equatorial proton (axial alcohol) occurred again at δ 3.83 (Figure 7); however, only a trace of the axial proton could be seen at δ 3.25. This confirms our findings that platinum oxide reductions yielded the axial alcohol only.

VII CONFORMATION OF N-METHYL-4-PIPERIDINOL, N-METHYL-3-PIPERIDINOL AND THEIR DERIVATIVES

In these compounds no configurational isomer exists, but the question of preferred conformation is of interest; at room temperature chair and flexible forms of the molecule will be freely interconverting. Some of the possible conformers are shown in Scheme IV.



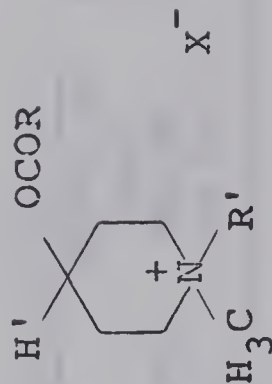
Scheme IV Some Possible Conformers of N-Methyl-4-piperidinol and its 3-Hydroxy Analog

The most favoured conformers would be expected to be (82), and (84) with the two substituents equatorial. This is confirmed for the 4-piperidinols by the fact that the base width of the 4-methine PMR signal (25.7 Hz at 40°C) (Chen and LeFevre 1965b) is close to the value anticipated if the proton

is axial. If the population of (82) were very close to 100% the 4-H base width should be 30.6 Hz, a value based on the J_{aa} and J_{ae} value derived from rigid models (Chen and LeFevre, 1965b) and from this data the population of (82) is calculated to be about 80% at 40°C. The population of the boat form (83a) must be very low because Hite et al. (1960) showed that N-methyl-4-piperidinol did not exhibit intramolecular hydrogen bonding. In all derivatives of N-methyl-4-piperidinol examined (Table X), the width of the 4-methine proton signal is between 26 and 29 Hz showing that conformers with equatorially oriented oxygen functions preponderate without exception. A similar result was found for N-methyl-3-piperidinol (4-methine base width 27 Hz) but in this case Hite et al. (1960) did find intramolecular hydrogen bonding, evidently due to the minor conformer (85). The spectrum of acetate of the 3-piperidinol (free base) also displayed a broad 3-H signal (base width 28 Hz), but the signal was distinctly narrow (base width 20 Hz) in the spectrum of the hydrochloride salt (solvent $CDCl_3$). In addition, the latter spectrum showed duplicate NMe (HNMe coupling) and OCOMe singlets of about equal intensities. The HNMe doublets collapsed to singlets in the presence of D_2O . This result is evidence that epimeric conjugate acids arise in similar amounts when the basic ester is protonated, represented by structures (86a) and (86b) in their most probably conformations. The population of the inverted chair of epimer (86b), i.e. (86c), cannot be high since, if it were, the 4-methine signal would not be so narrow. Signals

TABLE X

PMR CHARACTERISTICS OF N-METHYL-4-PIPERIDINOL AND DERIVATIVES



R	R'	X	Characteristics of H'			Characteristics of N-Me		
			Position from TMS in δ	Base width in Hz	Width at half height in Hz	Position from TMS in δ	Characteristics	Solvent
(a)	-	-	3.61	28	14	2.25	singlet	CDCl ₃
(b)	-	-	3.86	26	13	3.21	singlet	DMSO-D ₆
CH ₃	H	Cl	5.18	27	12	2.91-2.84	doublet	CDCl ₃
CH ₃	-	-	4.81	28	14	2.35	singlet	CDCl ₃
CH ₃	H	Cl	4.86	29	15	2.71	singlet	DMSO-D ₆

continued

TABLE X (continued)

PMR CHARACTERISTICS OF N-METHYL-4-PIPERIDINOL AND DERIVATIVES

R	R'	X	Characteristics of H'			Characteristics of N-Me		
			Position from TMS in δ	Base Width in Hz	Width at half height in Hz	Position from TMS in δ	Characteristics	Solvent
CH ₃	H	Cl	5.10	28	14	2.85	Singlet	D ₂ O
CH ₃	CH ₃	I	4.85	26	14	3.16-3.11	doublet	DMSO-D ₆
CH(Ph) ₂	H	Br	5.10(c)	27	13	2.63-2.55	doublet	CDCl ₃
CH(Ph) ₂	CH ₃	I	4.98	27(c)	12	3.26-3.08	doublet	DMSO-D ₆
C(OH)(Ph) ₂	H	Cl	(d)	29	13	2.96	singlet	D ₂ O
C(OH)(Ph) ₂	CH ₃	I	5.03	28	12	3.08-3.03	doublet	DMSO-D ₆

(a) - N-methyl-4-piperidinol.

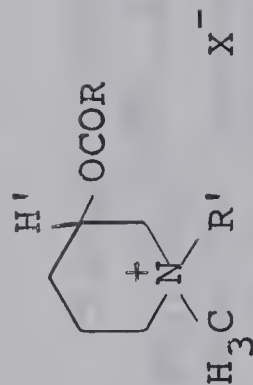
(b) - N-methyl-4-piperidinol methiodide.

(c) - overlaps with methine proton of diphenylacetate

(d) - obscured by D₂O signal.

TABLE XI

PMR CHARACTERISTICS OF N-METHYL-3-PIPERIDINOL AND DERIVATIVES



R	R'	X	Characteristics of H'			Characteristics of N-Me			OCOME		
			Position from TMS in δ	Base width	Width at half height	Position from TMS in δ	Characteristics	Position from TMS in δ	Characteristics	Position from TMS in δ	Characteristics
(a)	-	-	3.98	27.0	13	2.73	singlet	-	-	-	CDCl ₃
(b)	-	-	4.01	26.0	14.5	3.20-3.12	doublet	-	-	-	DMSO-D ₆
CH ₃	H	Cl	5.10	20.0	12	4.61-4.58 4.55-4.50	quartet	2.23-2.05	doublet	2.23-2.05	CDCl ₃
CH ₃	-	-	5.08	27.0	13	2.67	singlet	2.10	singlet	2.10	CDCl ₃
CH ₃	H	Cl	5.03	30.0	13	2.75	singlet	2.06	singlet	2.06	DMSO-D ₆
CH ₃	CH ₃	I	5.10	28.0	15	4.85-4.83	doublet	2.07	singlet	2.07	DMSO-D ₆
CH(Ph) ₂	H	Cl	5.20	28(c)	15	2.70	singlet	-	-	-	DMSO-D ₆

continued

TABLE XI (continued)

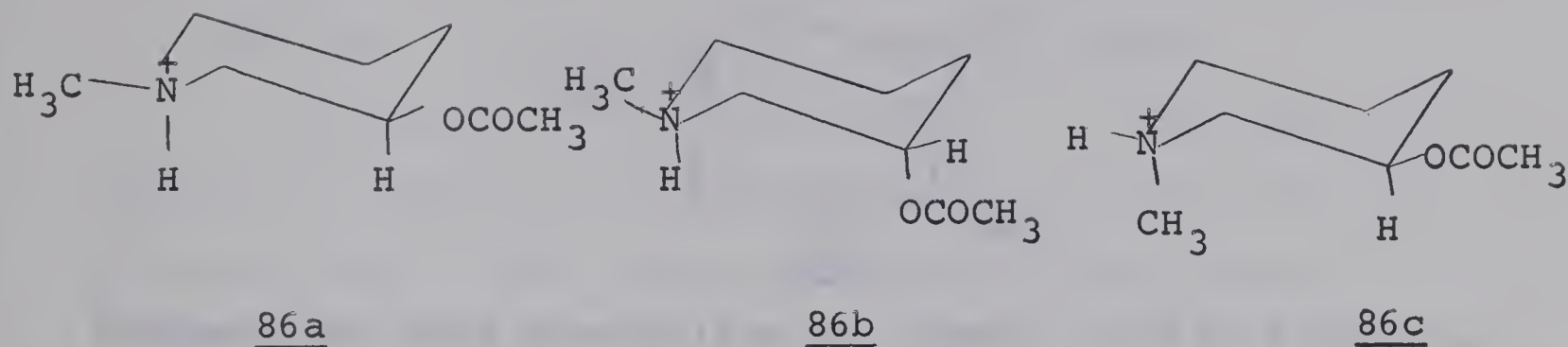
PMR CHARACTERISTICS OF N-METHYL-3-PIPERIDINOL AND DERIVATIVES

R	R'	X	Characteristics of H'			Characteristics of N-Me		OCOMe		
			Position from TMS in δ	Base width	Width at half height	Position from TMS in δ	Characteristics	Position from TMS in δ	Characteristics	Solvent
CH(Ph) ₂	CH ₃	I	5.25	(c)	10	3.11-2.93	doublet	-	-	DMSO-D ₆
C(OH)(Ph) ₂	H	Cl	5.13	20	7	2.58	singlet	-	-	DMSO-D ₆
C(OH)(Ph) ₂	CH ₃	I	5.28	25	13	4.78-4.51	doublet	-	-	DMSO-D ₆

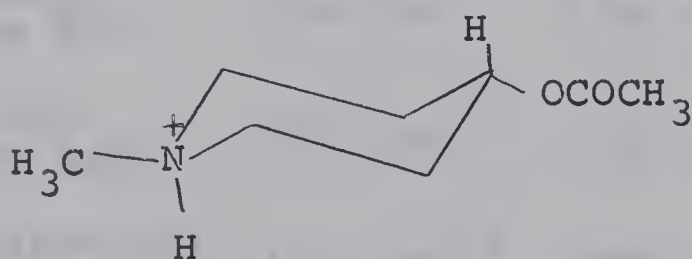
(a) - N-methyl-3-piperidinol.

(b) - N-methyl-3-piperidinol methiodide.

(c) - overlaps with 4-methine proton of diphenylacetate

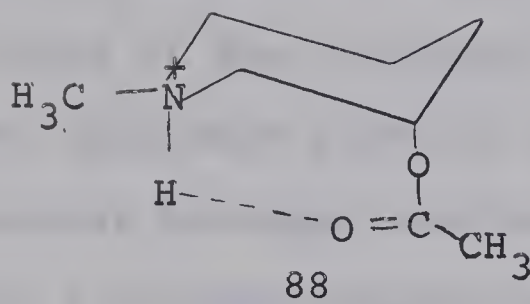


due to discrete epimers were not seen when the salt was dissolved in DMSO-D₆, and the 4-H signal width (30 Hz) showed that the epimer with an equatorial oxygen function preponderated as usual in this solvent. Evidence for epimeric conjugate acids was also seen in the spectrum of the 4-acetoxy-N-methyl-4-piperidinol hydrochloride in CDCl₃, but in this case the 4-H signal width (27 Hz) and the relative peak heights of the NMe and OCOMe signals showed the preponderance of isomer 87.



87

The higher population of the axial OCOMe form (86b) in the acetate of the 3-piperidinol salt might be due to intramolecular hydrogen bonding of type (88), acting as a stabilizing factor.



Evidence for this possibility was sought in that a bond as shown in (88) should lead to a lower $\nu_{\text{C=O}}$ value than that seen in the free base. It was found (Table XII):

TABLE XII

$\nu_{\text{C=O}}$ STRETCHING FREQUENCIES OF AMINO ALCOHOLS

Compound	Concentration		
	0.1%	0.3%	3.0%
N-Methyl-3-piperidyl acetate HCl	1745 cm.^{-1}	1745 cm.^{-1}	1745 cm.^{-1}
N-Methyl-3-piperidyl acetate Base	1730 cm.^{-1}	1730 cm.^{-1}	1725 cm.^{-1}
N-Methyl-4-piperidyl acetate HCl	1745 cm.^{-1}	1745 cm.^{-1}	1745 cm.^{-1}
N-Methyl-4-piperidyl acetate Base	1730 cm.^{-1}	1730 cm.^{-1}	1725 cm.^{-1}
α 1,3-Dimethyl-4-piperidyl acetate HCl	1740 cm.^{-1}	1740 cm.^{-1}	1740 cm.^{-1}
β 1,3-Dimethyl-4-piperidyl acetate HCl	1735 cm.^{-1}	1740 cm.^{-1}	1745 cm.^{-1}

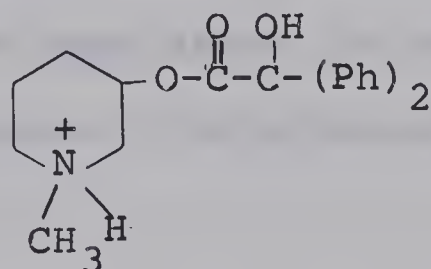
a) the $\nu_{\text{C=O}}$ of the 3-acetate hydrochloride and the 3-acetate free base did not vary significantly (measured at higher dilution so that intermolecular interaction

should not be important)

- b) that ν C=O of the 3-acetate did not differ significantly from the C=O values of the 4-acetate isomer.

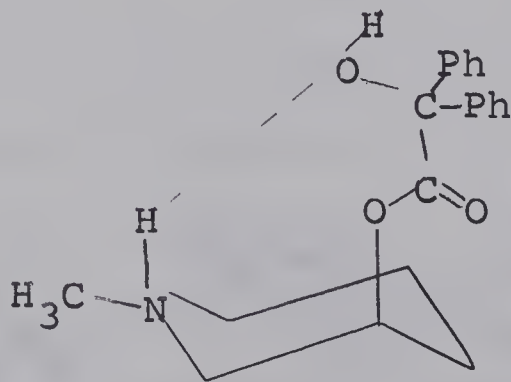
These results therefore provided no conclusive evidence for intramolecular hydrogen bonding effects in the hydrochloride of the 3-acetoxy-N-methyl-piperidinols.

The spectrum of the benzilate hydrochloride (89)



89

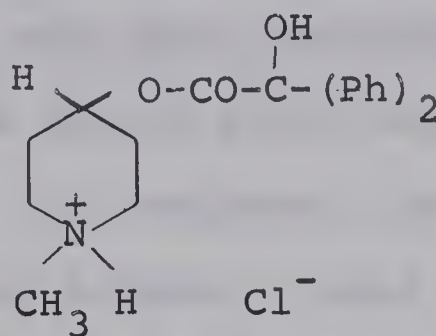
of the 3-piperidinol also displayed a narrow 3-methine signal (base width 20 Hz), a result which suggests an increased preference for the axial ester conformer (90) possibly stabilized by an intramolecular bond as shown in (90). Steric



90

considerations and the ability to form such a bond in the corresponding methiodide salt are reflected in the wider 3-H PMR signal (base width 25 Hz) of the latter salt.

In the hydrochloride of the 4-benzilate (91), where intramolecular bonding of the type shown in (90) is not possible,

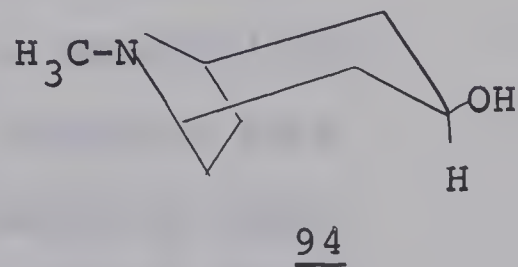
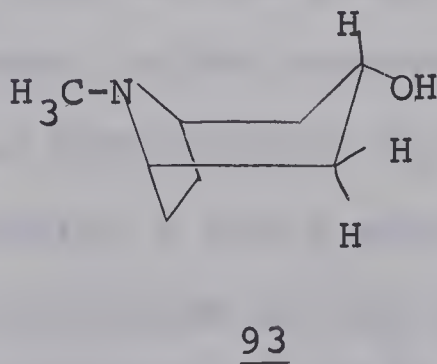
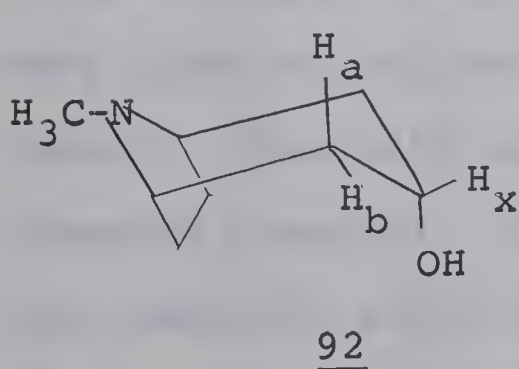


91

the 4-methine PMR signal had a base width (29 Hz) characteristic of the usual preponderance of the equatorial ester conformation.

VIII CONFORMATION OF TROPINE, PSEUDOTROPINE AND THEIR ESTERS

Two studies have been directed at solving the question of whether the piperidine ring of tropine exists in a preferred chair (92), or boat conformation (93) (Chen and LeFevre, 1965b; Bishop et al., 1966). The most valuable information in this



respect derives from the C-3 proton signal of tropine. This

is analysed as the X portion of two ABX systems, and the small value of its base width (17 Hz, 60 MHz spectrum), equal to $2(J_{ax} + J_{bx})$, shows that its spin-spin coupling cannot involve a large J_{vic} value as should arise between eclipsed protons of the boat form (93). In contrast, the 3-methine signal of pseudotropine is far broader (base width 40 Hz) as expected for an axial orientation as in (94) (the actual widths are evidence of ring deformation, Sinnema et al. 1968).

It is of interest to discover whether the chair (92) continues to be favoured over the boat (93) when the hydroxyl function of tropine is esterified, particularly with bulky acids such as tropic (as in atropine) and benzoic. In these esters interactions between the axial ester function and the 2,6-bimethylene bridge might significantly raise the energy of the chair form (92). For this reason the PMR spectrum of tropyl acetate, tropyl benzoate and atropine and of corresponding pseudotropine derivatives (not pseudotropyl tropate) were recorded and compared with spectra of the free alcohols (Table XIII). It is to be noted that the 3-methine signals of the tropyl esters all fall in the range 15-16 Hz, i.e. very close to values as seen in the spectrum of tropine itself. This also applies when solvent D_2O is employed (see atropine example). Therefore, a bulky ester function does not radically alter the preference of the piperidine ring of tropine for a chair conformation. This must be a result of the ester function itself being too far removed from the

TABLE XIII

PMR CHARACTERISTICS OF ATROPINE, TROPINE, PSEUDOTROPINE AND THEIR DERIVATIVES

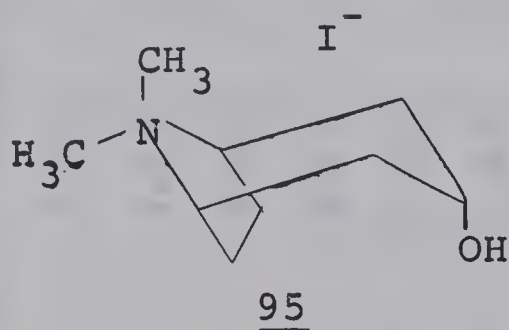
Compound	Form	Position From TMS in δ	Width at Half Height in Hz	C-3 Base Width in Hz	Solvent
Tropine	Base	3.90	10.5	16.0	CCl ₄
Tropine	Base	3.95	12.0	(a)	CDCl ₃
Tropine	Base	3.81	13.5	15.0	DMSO-D ₆
Tropine	Base	4.23	10.5	17.0	Pyridine
Tropine	Methiodide	5.10	11.0	16.0	DMSO-D ₆
Tropyl acetate	Hydrochloride	5.17	11.0	15.0	CDCl ₃
Tropyl acetate	Hydrochloride	5.04	9.5	14.5	D ₂ O
Tropyl benzilate	Hydrochloride	5.09	10.0	16.0	DMSO-D ₆
Tropyl benzilate	Hydrochloride	5.28	10.0	14.0	D ₂ O
Tropyl benzilate	Methiodide	5.16	8.5	14.0	DMSO-D ₆
Pseudotropine	Base	3.73	18.0	26.0	CCl ₄
Pseudotropine	Base	3.88	19.0	25.5	CDCl ₃

continued

piperidine ring to clash with the bimethylene bridge. The 3-methine characteristics of esters of pseudotropine were as anticipated, very similar to those of pseudotropine itself (see Table XIII).

Other points of interest concerning these spectra are as follows:

1) In tropine the C-3 proton signal is more down field than that of pseudotropine as we would expect. The PMR spectrum of tropine methiodide (95) in DMSO-D₆ shows the expected coupling of the hydroxyl proton. The J value is



4 Hz and it occurs at δ 4.85. In comparing this with β -1,3-dimethyl-4-piperidinol methiodide, J value 4 Hz and it occurs at δ 4.93. This is further proof that the hydroxyl group is axial. The spectrum of pseudotropine methiodide should be run as a comparison; it is, however, insoluble in DMSO-D₆.

2) In pyridine the spectrum of tropine (Figure 8) and pseudotropine (Figure 9), several signals are shifted down field compared to their position in CDCl₃ or CCl₄.

a) the hydroxyl group is shifted well down field from the resonance position in CCl₄.

TABLE XIII (continued)

PMR CHARACTERISTICS OF ATROPINE, TROPINE, PSEUDOTROPINE AND THEIR DERIVATIVES

Compound	Form	Position From TMS in δ	Width at Half Height in Hz	C-3 Base Width in Hz	Solvent
Pseudotropine	Base	3.68	21.0	24.0	DMSO-D ₆
Pseudotropine	Base	4.13	18.0	27.0	Pyridine
Pseudotropyl acetate	Hydrochloride	5.11	18.5	24.0	CDCl ₃
Pseudotropyl acetate	Hydrochloride	5.14	20.5	26.0	D ₂ O
Pseudotropyl benzilate	Hydrochloride	5.20	21.0	27.0	DMSO-D ₆
Pseudotropyl benzilate	Hydrochloride	5.47	20.5	26.0	D ₂ O
Pseudotropyl benzilate	Methiodide	5.21	20.5	26.5	DMSO-D ₆
Atropine	Sulfate	5.03	9.5	16.5	D ₂ O

(a) - obscured by hydroxyl signal

b) The C-3 proton is shifted more down field and is better resolved.

c) The ring protons are more resolved.

3) In the free base in DMSO-D₆ the hydroxyl proton is broadened as expected and in the methiodide the hydroxyl proton is resolved.

4) Protonated epimers as obtained by Closs (1961) were also observed in the acetoxy esters.

TABLE XIV
PROTONATED EPIMERS OCCURING
IN THE ACETOXY ESTER HYDROCHLORIDES
OF TROPINE AND PSEUDOTROPINE

Compound	Character- istics	Position δ		Solvent
		of larger doublet	of small doublet	
Tropine acetate hydrochloride	2 doublets	2.76-2.85	2.96-3.15	CDCl ₃
Pseudotropine acetate hydrochloride	2 doublets	2.76-2.86	2.91-3.03	CDCl ₃

The doublets which occurred in the hydrochloride salt disappeared when ammonia was added (thus removing the proton) or when D₂O was added (thus facilitating rapid proton exchange). This proves that protonated epimers had occurred

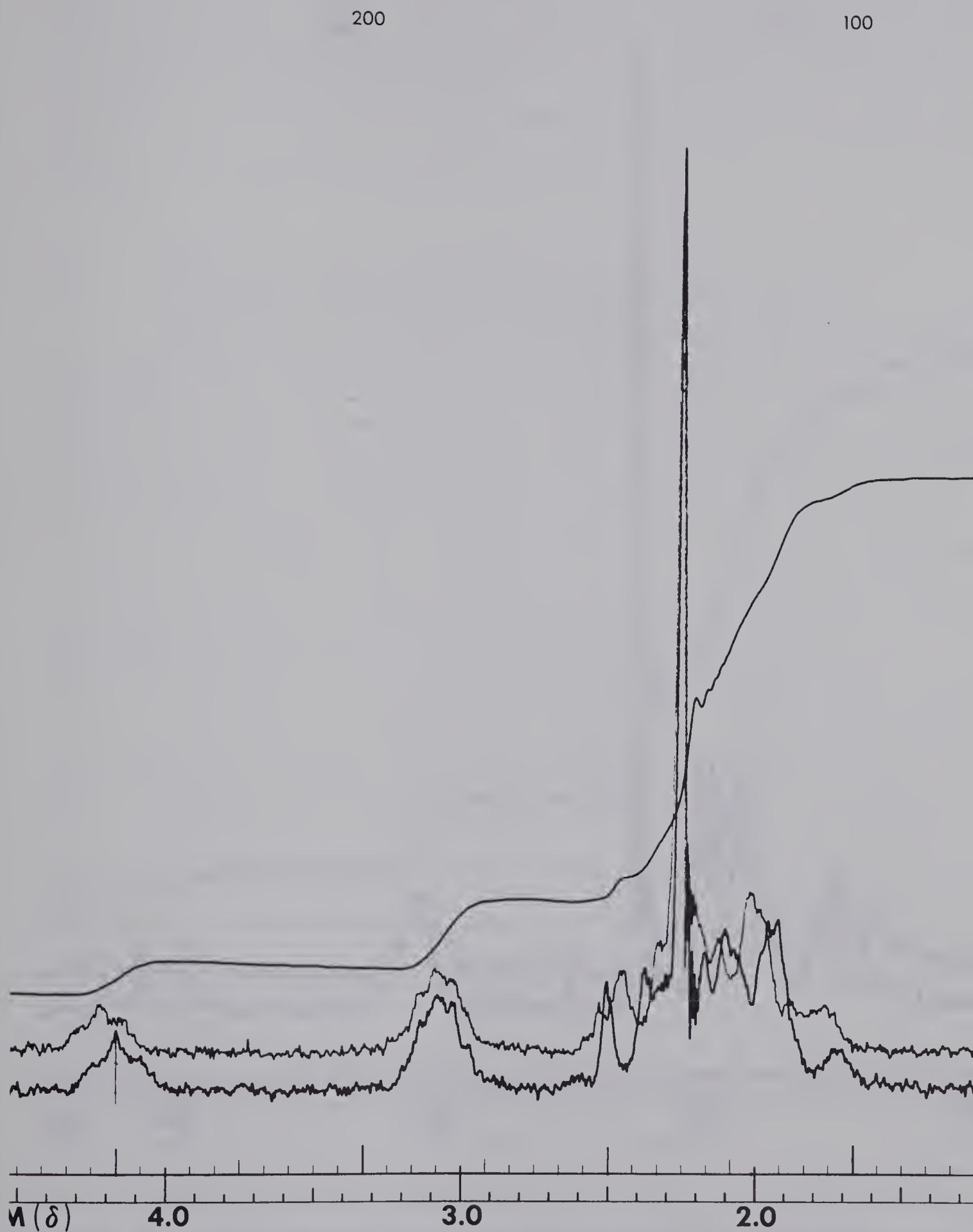


Figure 8. PMR Spectrum of tropine in pyridine

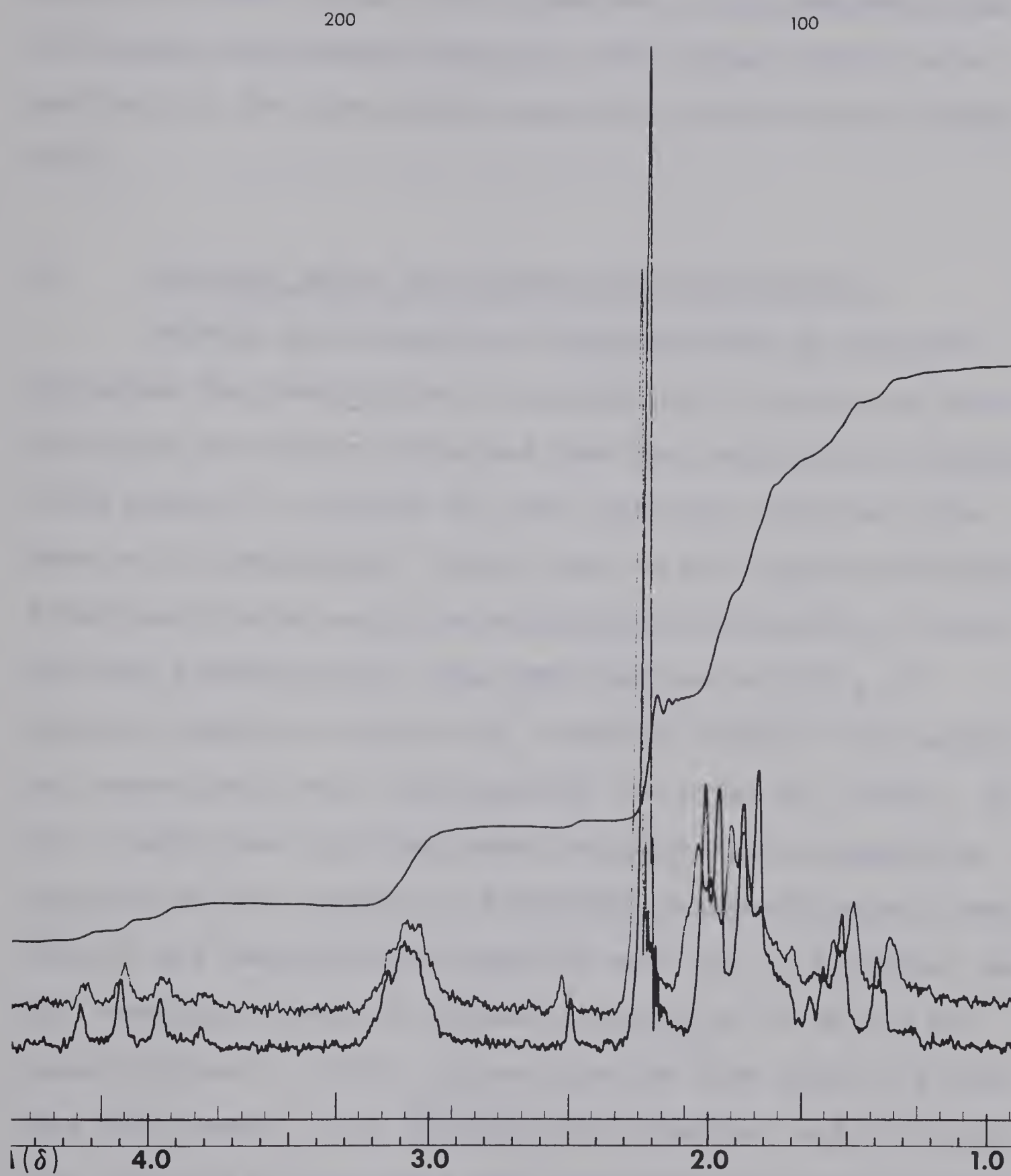


Figure 9. PMR Spectrum of pseudotropine in pyridine

in these salts. The larger doublet always occurred upfield, similar to what Closs (1961) observed in the hydrochloride of tropine and pseudotropine, and this larger doublet was assigned to the more stable equatorial methyl group (Closs, 1961).

IX ISOMERIC RATIO OF TROPINE AND PSEUDOTROPINE

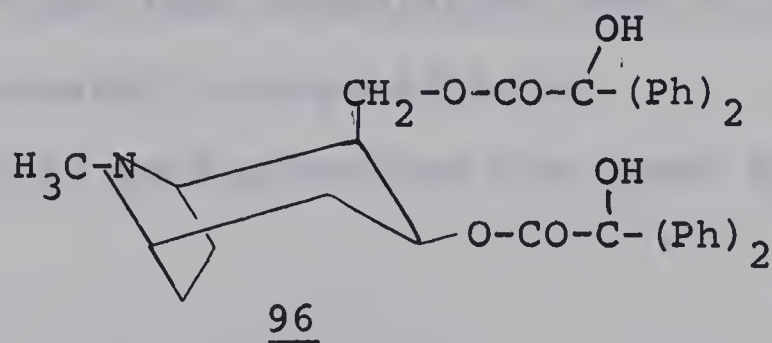
Beckett and co-workers (1959a) devised an infrared procedure for determining the presence of tropine and pseudotropine in mixtures obtained from the reduction of tropinone. A PMR method of analyses for the tropinone reduction products was investigated. Again here we were hoping that both 3-methine protons would be sufficiently far apart to allow separate investigation. The PMR spectrum in CDCl_3 of reduced tropinone showed both 3-methine signals overlapping, and these again were overlapped by the hydroxyl proton. It was thought that pyridine might separate these signals as occurred in the isomeric 1,3-dimethyl-4-piperidinols. Pure tropine and pseudotropine spectrum were run in pyridine, and the 3-methine proton of tropine occurred at $\delta 4.10$ and of pseudotropine at $\delta 4.09$. It was obvious then that if a mixture was present, both protons would overlap, and the reduction products of tropinone were therefore not run in pyridine.

The quaternary salt of the crude reduction product of tropinone was made in the hope that we could differentiate the N-methyl groups and calculate the percentage of isomers

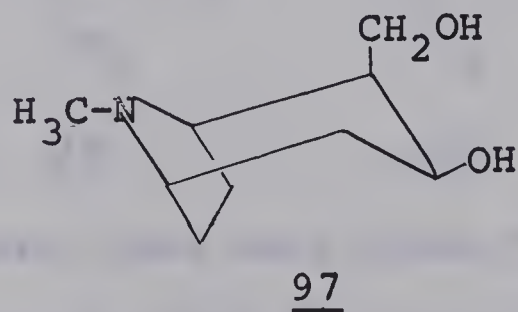
by peak height measurement. However, only three N-methyl signals occurred (two overlapping), and we could not determine which signal belonged to which isomer. Therefore the attempt at finding a PMR method of analysis of isomeric tropan-3-ol mixtures was abandoned.

X DERIVATIVES OF COCAINE

It was of interest to us to try to synthesize the following compound (96) with two benzilic acid groups instead of one to see if it would be a more potent anticholinergic.



Cocaine was reduced with lithium aluminium hydride (Fador, 1960) to yield the 2-hydroxymethyl-3- β -tropanol (97).



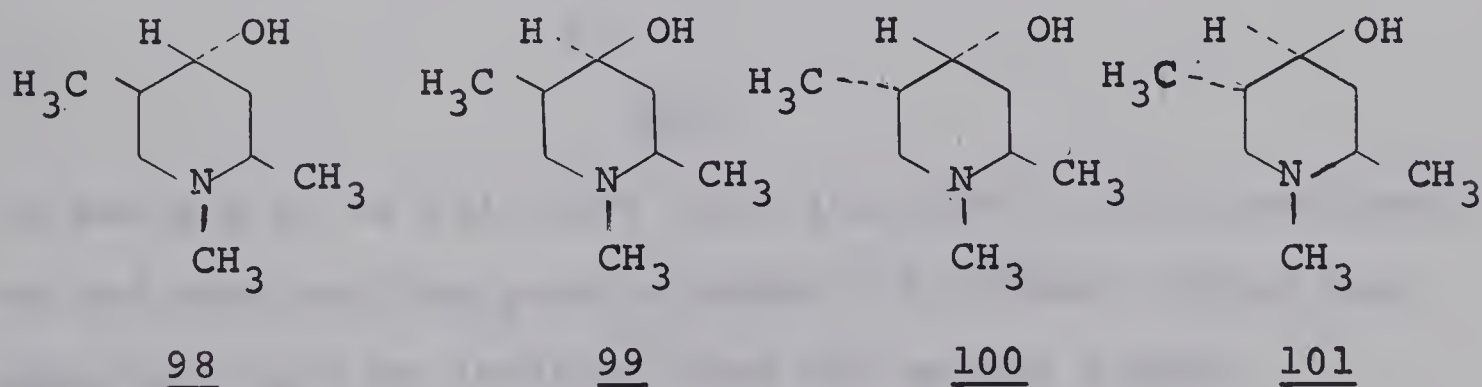
This was then esterified with two moles of methyl benzilate by the procedure of Cannon (1960) to yield the desired

compound, 2-benzilatemethyl-3-tropanylbenzilate (96) in a very low yield of 11%. The hydrochloride (96a) was made in the usual manner and the analysis was correct for this compound. All attempts to form the methiodide failed, as might have been expected from the axial nature of the 2-substituent.

XI 1,2,5-TRIMETHYL-4-PIPERIDINOL DERIVATIVES

Narzov in 1964 synthesized the title compound from 2,5-dimethyl-4-piperidone. He reduced 2,5-dimethyl-4-piperidone by various procedures obtaining three of the four possible isomers and then methylating them to obtain the isomeric 1,2,5-trimethyl-4-piperidinols.

The four possible configurations are shown in formulae (98)-(101).



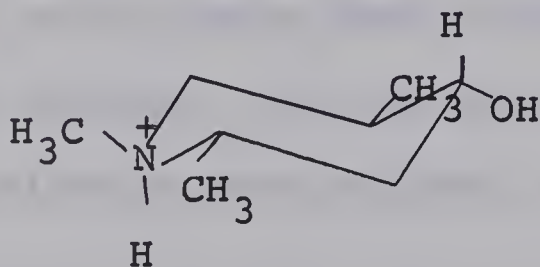
No configurational data were given for these compounds. The α -form gave a hydrochloride of m.p. 196°; no hydrochlorides were mentioned for the other forms.

A sample of 1,2,5-trimethyl-4-piperidone was donated

to us and we carried out a few reduction experiments to obtain the isomeric alcohols.

The ketone was initially reduced with lithium aluminium hydride; the PMR spectra of the product showed that we had obtained a mixture of isomers of 1,2,5-trimethyl-4-piperidinol.

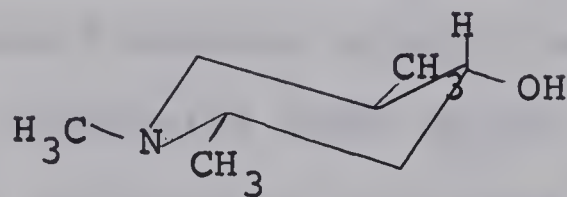
We then made the hydrochloride (102) of the crude reduced material, and we obtained 10 g of a solid (33%) which after purification melted at 192-194°C (lit 195-196°C). Therefore we had isolated the α -form. The PMR spectra confirmed the purity of the isomer. Signals of the secondary methyl groups were clean doublets occurring at δ 1.03 and 1.4 in D₂O. The free base was liberated and the picrate was made.



It had a m.p. of 141-143°C (lit 142-143°C); this confirmed we had obtained the pure α -isomer. No other crystalline material could be isolated from the mother liquor.

The methiodide was then made from the total crude reduction product and again from PMR data we had obtained a mixture of isomers. After repeated crystallization one pure isomer was obtained (103). The secondary methyl groups were

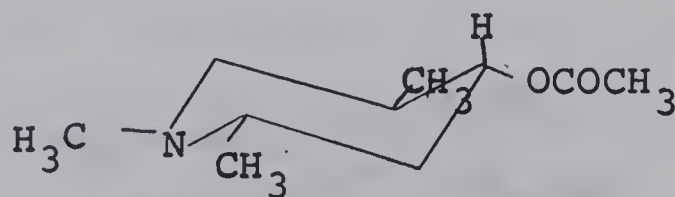
sharp doublets occurring at $\delta 1.1$ and 1.45 in D_2O . They were



103

almost identical to the position in the hydrochloride, so again we probably obtained the α -isomer. From the mother liquor we obtained many different fractions of crystals, and the PMR evidence confirmed a mixture of isomers. All attempts to isolate a second pure isomer by fractional crystallization failed.

The methyl esters were then prepared using acetyl chloride in ethyl acetate. In the PMR spectra of total acetate two methine signals were evident; one very wide and one



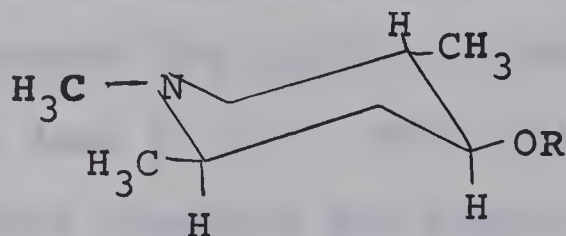
104

very narrow (16 and 28 Hz), again confirming the presence of a mixture of isomers. Fractional crystallization of the

hydrochloride failed. The free base was liberated and the methiodide was made in the usual manner. On fractional crystallization from alcohol one pure isomer (104) was obtained, with a wide 4-methine signal (base width 28 Hz); thus confirming an equatorial OCOMe group. The secondary methyl group signal occurred at $\delta 0.93$ and $\delta 1.35$.

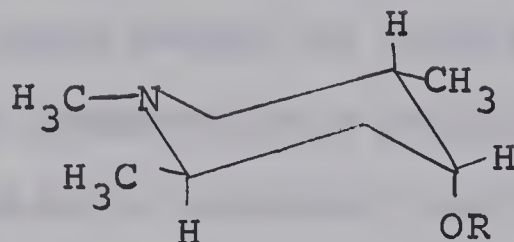
Again from the total crude reduction product the benzilate ester was made. The oil which was obtained solidified on standing. The PMR evidence again confirmed the presence of two isomers. Repeated recrystallization from alcohol-water yielded one pure isomer (base width 29 Hz). The PMR spectra confirmed the presence of an equatorial ester. Signals due to the methyl groups occurred at $\delta 0.60$ and $\delta 1.01$ in DMSO-D₆. The hydrochloride and the methiodide were made and again the PMR spectra confirmed the presence of only one isomer.

No conclusive configurational assignments were made to the pure compounds isolated, but it is probable that they all have the stereochemistry (105) with all substituents equatorial. The equatorial orientation of the ester function is confirmed



105

for the pure acetate and benzilate by the broad nature of the



106

4-H signal (base width ~28 Hz). The axial ester (106) is probably the next most abundant isomer produced, since the characteristic 4-H signal is clearly resolvable in the spectrum of the total acetate and benzilates.

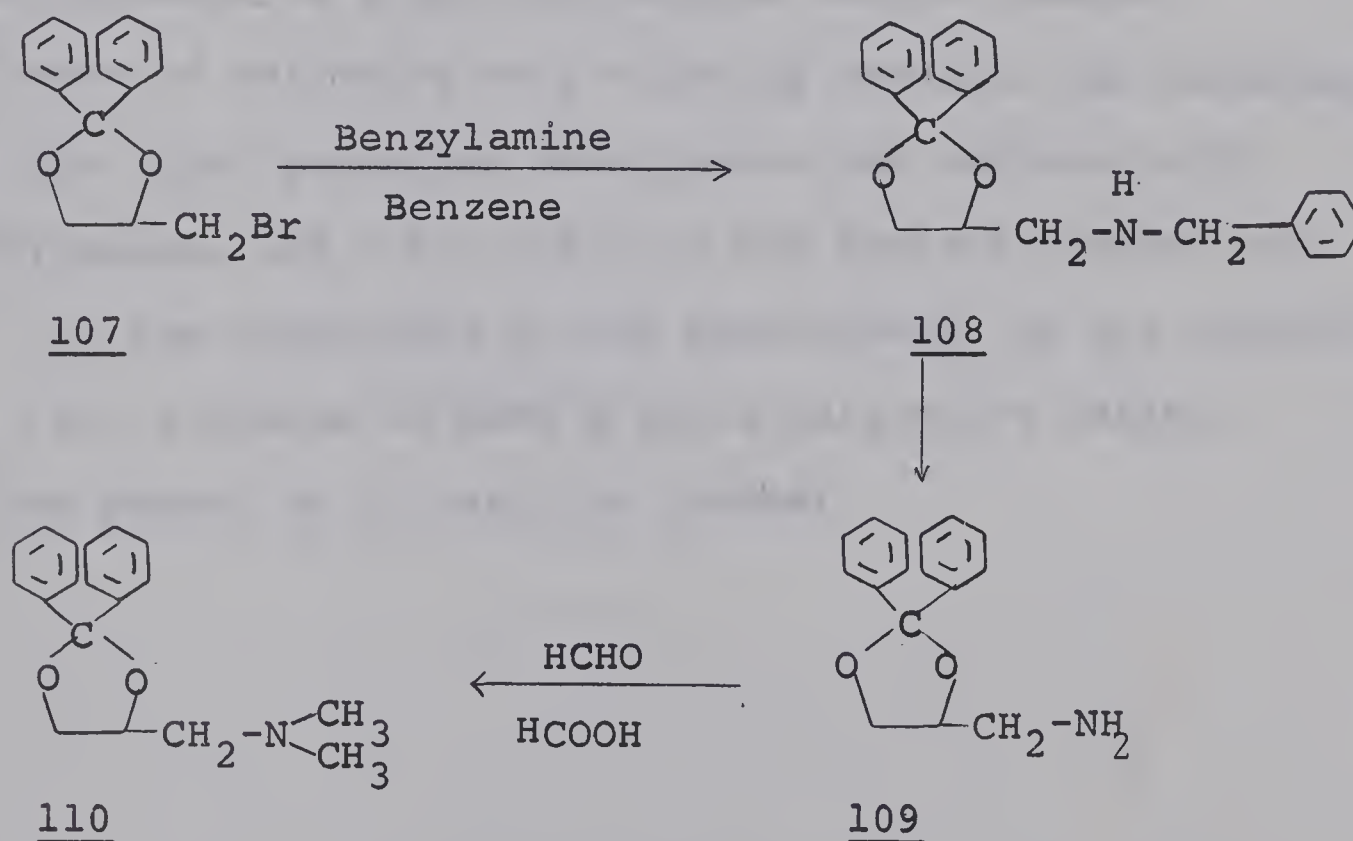
XII 2,2-DIPHENYL-4-DIMETHYLAMINOMETHYL-1,3-DIOXOLANE

Blicke (1952) synthesized the title compound and Brown and Werner (1949) tested it for antispasmodic activity and found it to be almost as active as atropine. This compound contains an asymmetric centre and could be resolved into its optical isomers. It was of interest, therefore, to compare the activities of the enantiomers in view of activity differences seen between the optical isomers of other asymmetric spasmolytics (see p. 5). With this in mind we set out to synthesize this compound and resolve it into its optical isomers and have the isomers tested.

Blicke (1952) synthesized the title compound by reacting 2,2-diphenyl-4-bromomethyl-1,3-dioxolane (which was

synthesized from benzophenone, and epibromohydrin) with anhydrous dimethylamine under pressure.

2,2-Diphenyl-4-bromomethyl-1,3-dioxolane (107) was synthesized in the same manner as Blicke (1952). We attempted to obtain the title compound by a modification of the method of Blicke which avoided a pressure reaction. The following scheme was devised (Scheme V).



Scheme V Attempted Synthesis of 2,2-Diphenyl-4-dimethylaminomethyl-1,3-dioxolane

In the first step (107) was reacted with benzylamine in benzene for 48 hours at reflux temperature. No product could be isolated. This procedure was again tried using an excess of sodium carbonate. This procedure yielded a small

amount of the required product (108). The hydrochloride salt (108a) was then made and we obtained a 7% yield of the desired compound. Resolution with d-10-camphorsulfonic acid, tartaric acid and benzoyl tartaric acid in acetone-ether mixture failed (no solid diastereoisomeric salts formed). Due to the poor yield this procedure was abandoned.

It was then attempted to obtain the product by refluxing the bromodioxolane (107) dissolved in alcohol with anhydrous dimethylamine in a dry-ice acetone reflux chamber. After 24 hours of refluxing only starting material was obtained.

In the first procedure benzylamine was replaced with benzylmethylaniline, and a 60% yield of the desired product was obtained. It was identified by PMR spectroscopy as the correct compound. All attempts to make a solid derivative failed. Time did not permit us to carry on further.

PHARMACOLOGY

METHODS

A. Measurement of Anticholinergic Activity

1. pA_2 Values

pA_2 values (Schild, 1947) were determined on guinea pig ileum. The guinea pigs were killed by breaking their necks. Segments of ileum 2-3 cm were removed from points adjacent to the ileocecal junction. The segments were suspended in Krebs solution at 37°C gassed with 95% O_2 /5% CO_2 in the conventional manner. Contractions were recorded using an isotonic ink-writing lever. At least three concentrations of antagonist were used to determine each pA_2 value. The relative potencies were calculated in the following manner: the pA_2 value for atropine was subtracted from the pA_2 value of the drug, and the antilog of this difference gave the relative potency. Specificities were calculated by determining the ratio of the anticholinergic activity to the antihistaminic activity.

2. Mydriasis

Male or female albino mice (15-20 g) were used. Drugs were dissolved in distilled water and injected subcutaneously. The procedure of Karlen (1970) was used to determine mydriatic activity. Eight mice were used at each of three dose levels and pupil diameters

were measured at 30 minutes and 24 hours after each dosing. The percent increase in eye pupil diameter compared with control was plotted versus the log dose: from this the ED_{50} (that dose of drug which increases the eye pupil diameter 1.5 times over control) was calculated.

3. Antioxotremorine activity

The mice used to determine mydriasis were also used for this experiment. The procedure of Karlen (1970) was used to assess the inhibition of tremors. Oxotremorine (50 μ g) was injected subcutaneously to induce tremors which were assessed after 30 minutes.

B. Measurement of Cholinergic Activity

1. Rat Blood Pressure

Male rats (150-300 g) were anesthetized with urethane (1.875 g/kg) injected intraperitoneally. The trachea was cannulated and arterial blood pressure was recorded using an E & M pressure transducer, type P-1000A connected to an E & M physiograph type DMP-4A. Drugs were dissolved in 0.9% saline and injected through a polythene cannula inserted into a femoral vein.

Drugs used: atropine sulfate (B.D.H.), orphenadrine hydrochloride (Riker), ethopropazine hydrochloride

(Poulenc), acetylcholine (B.D.H.), hyoscine hydrobromide (B.D.H.), urethane (B.D.H.). Solutions used:

Krebs: NaCl, 6.9 g; KCl, 0.35 g; $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$, 0.55 g; KH_2PO_4 , 0.16 g; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 0.29 g; dextrose, 1.0 g; NaHCO_3 , 2.1 g; distilled water to 1 litre.

RESULTS

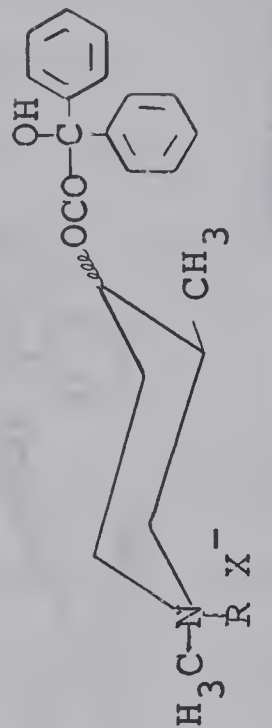
A. Anticholinergic Activity of 1,3-Dimethyl-4-Piperidyl Derivatives

1. pA_2 Values

The β -isomers, compounds (66) to (69) were more potent anticholinergic agents than the α -isomers, compounds (60) to (63) when tested on guinea pig ileum. Compounds (68) and (69), the β -benzylates, were 2-3 times more active than the α -benzylates (62) and (63), while compounds (66) and (67), the β -diphenylacetates, showed little difference in potency from the α -diphenylacetates, compounds (62) and (63). The α - and β -benzylates, compounds (62), (63), (68) and (69) were 5-10 times more potent than the corresponding α - and β -diphenylacetates, compounds (60), (61), (66) and (67). The pA_2 values, against histamine, showed that all these compounds were at least as specific as atropine as anticholinergic agents. Quaternization had little effect on potency.

TABLE XV

ANTICHOLINERGIC, ANTIHISTAMINIC, MYDRIATIC AND ANTIOXOTREMORINE ACTIVITY

OF α - AND β -1,3-DIMETHYL-4-PIPERIDYL BENZILATES α -isomer (trans OCOR/CH₃) β -isomer (cis OCOR/CH₃)

No.	pA ₂ Ach	Relative Potency	Relative ^e Potency	pA ₂ histamine	Relative ^f Potency	Speci- ^g ficity	Mydriatic ^h Activity	Antioxotremorine activity	
								mM/kg	% decrease in tremors
62 ^a	8.01	126		<5.60	<489	0.25	0.0016	0.0016	10
63 ^b	7.49	97		<5.70	<616	0.15	0.0014	0.0014	25
68 ^c	8.45	347		<5.60	<489	0.70	0.0011	0.0011	25
69 ^d	8.38	295		<5.70	<616	0.50	0.0004	0.0004	25

a - α isomer, R = H; X = Clb - α isomer, R = CH₃; X = Ic - β isomer, R = H; X = Cld - β isomer, R = CH₃; X = I

e - atropine = 1000

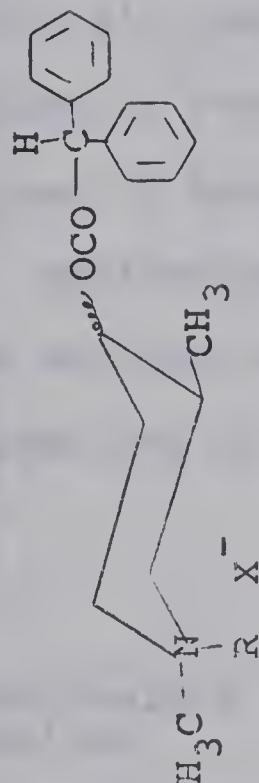
f - atropine = 1000

g - pA₂Ach/pA₂ hist.h - ED₅₀ in mM/kg

TABLE XVI

ANTICHOLINERGIC, MYDRIATIC AND ANTIOXOTREMORINE ACTIVITY

OF α - AND β -1,3-DIMETHYL-4-PIPERIDYL DIPHENYLACETATES



Compound No.	Isomer	R	X	pA ₂ Ach	Relative Potency atropine = 1000	Mydriatic activity ED ₅₀ in mM/kg	Antioxotremorine activity	
							mM/kg	% decrease in tremors
60	α	H	Cl	7.34	27	0.0086	0.0097	10
61	α	CH ₃	I	7.62	52	0.0062	0.0075	25
66	β	H	Cl	7.68	59	0.0075	0.0097	25
67	β	CH ₃	I	7.62	51	0.0055	0.0075	25

2. Mydriasis

In tests for mydriatic activity the β -benzilates, compounds (68) and (69), were slightly more active than the α -benzilates, compounds (60) and (61). Again the α - and β -benzilates, compounds (62), (63), (68) and (69) were 5 times more active than the corresponding α - and β -diphenylacetates, compounds (60), (61), (66) and (67). Quaternization of the nitrogen caused an increase in activity for all compounds. The duration of the mydriasis was less than 24 hours. The effect of atropine lasted for more than 36 hours.

3. Antioxotremorine Activity

The antioxotremorine activity of these compounds was very weak and no difference in isomer activity was observed.

B. Anticholinergic Activity of Tropine/Pseudotropine Derivatives

1. pA_2 Values

The tropine derivatives were 3 times more active than the pseudotropine derivatives. Quaternization of the nitrogen in tropine benzilates yielded a compound which was a more potent anticholinergic than atropine.

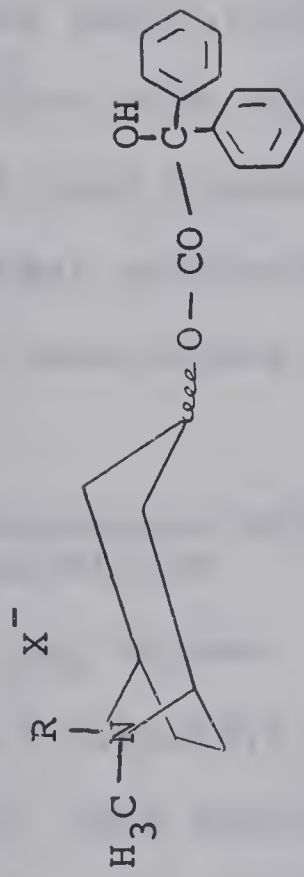
2. Mydriasis

All compounds were potent mydriatics with little

TABLE XVII

ANTICHOLINERGIC, MYDRIATIC AND ANTIOXOTREMORINE ACTIVITY

OF TROPINE AND PSEUDOTROPINE BENZILATE



Isomer	R	X	pA2 Ach	Relative Potency atropine = 1000	Mydriatic activity ED50 in mM/kg	Antioxotremorine activity	
						mM/kg	% decrease in tremors
α	H	Cl	8.51	398	0.0005	0.0007	75
α	CH ₃	I	8.50	389	0.0004	0.0006	75
β	H	Cl	8.81	794	0.0005	0.0004	50
β	CH ₃	I	8.93	1047	0.0004	0.0004	75

difference in activity. Quaternization had little effect on potency. The duration of action of these compounds was less than 24 hours in all cases.

3. Antioxotremorine Activity

Only one compound, the hydrochloride of tropine benzilate, was found to be active at the dose levels studied and quaternization decreased the potency. Friedman and Smith (1959) found that tropine benzilate was equiactive with atropine or slightly less active than atropine in many pharmacological tests; they also found it to be a potent antioxotremorine agent. We also came to these same conclusions.

C. Anticholinergic Activity of N-Methyl-3- and 4-Piperidyl Derivatives

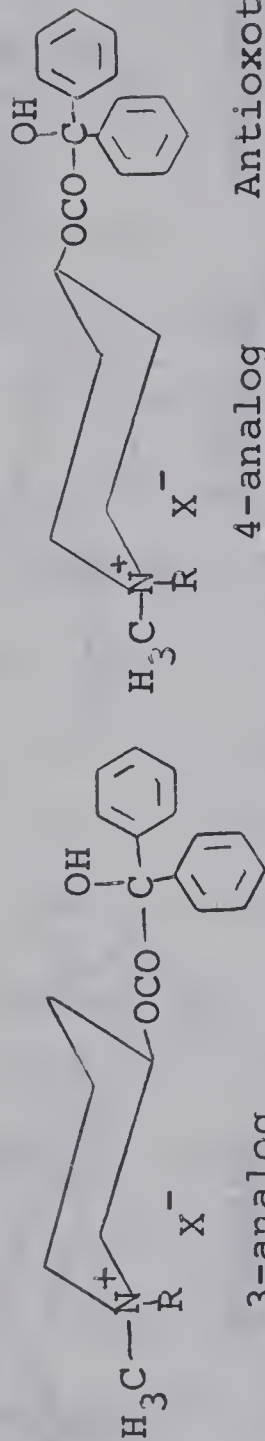
1. pA_2 Values

The 4-piperidyl derivatives, compounds (16), (17), (18) and (19) were more active than the 3-piperidyl derivatives, compounds (22), (23) and (25), except in one case, compound (24). This compound can exist in a similar conformation to atropine (see PMR discussion page 72) and this might account for its greater activity because the other compounds cannot exist in this conformation. Quaternization of the nitrogen led to a decrease in activity in all compounds except compound (23). The 3-

TABLE XVIII

ANTICHOLINERGIC, ANTIHISTAMINIC, MYDRIATIC AND ANTIOXOTREMORINE ACTIVITY

OF N-METHYL-3- AND 4-PIPERIDYL BENZILATES



No.	pA ₂ Ach	3-analog		4-analog		Antioxotremorine activity	
		Relative Potency	pA ₂ histamine	Relative ^f Potency	Specificity ^g Mydriatic ^h Activity	mM/kg in tremors	% decrease in tremors
18 ^a	8.96	1122	--	--	0.0003	0.0005	25
19 ^b	8.92	1023	--	--	0.0004	0.0004	25
24 ^c	9.10	1549	5.51	398	3.89	0.0003	25
25 ^d	8.71	630	5.60	489	1.28	0.0002	25

a - 4-analog; R = H; X = Cl
b - 4-analog; R = CH₃; X = I
c - 3-analog; R = H; X = Cl
d - 3-analog; R = CH₃; X = I
e - atropine = 1000
f - atropine = 1000
g - pA₂Ach/pA₂ hist.
h - ED₅₀ in mM/kg

TABLE XIX

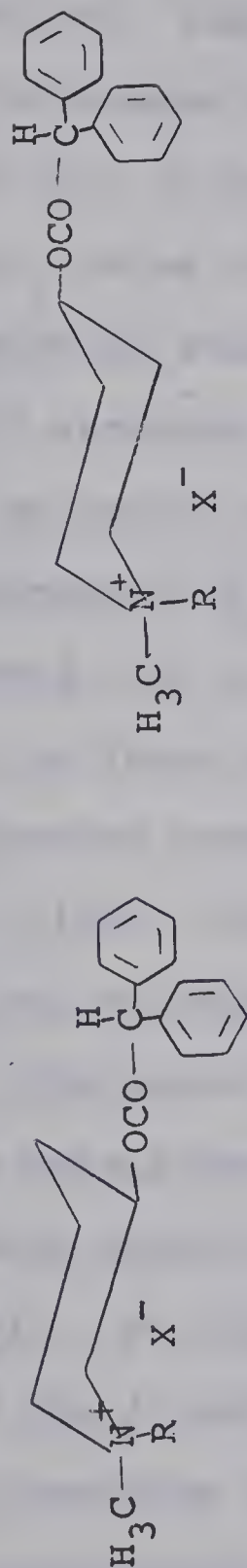
ANTICHOLINERGIC, ANTIHISTAMINIC, MYDRIATIC AND ANTIOXOTREMORINE ACTIVITY

OF N-METHYL-3 AND 4-PIPERIDYL DIPHENYLACETATES

Compound No.	3-analog			Relative ^e histamine pA ₂ Potency	Relative ^f Potency	4-analog		Antioxotremorine	
	pA ₂ Acn	Relative Potency	pA ₂			Mydriatic activity ED ₅₀ (mM/kg)	activity	mm/kg	% decrease in tremors
16 ^a	8.27	229	--	--	--	0.0009	0.0017	slight	
17 ^b	8.22	204	--	--	--	0.0007	0.0013	slight	
22 ^c	8.19	190	5.33	722		0.001	0.0017	slight	
23 ^d	8.22	204	5.47	561		0.001	0.0013	slight	

a - Analog 4; R = H; X = Br
 b - Analog 4; R = CH₃; X = I
 c - Analog 3; R = H; X = Cl
 d - Analog 3; R = CH₃; X = I

e - Atropine = 1000
 f - Atropine = 1000



and 4-piperidyl benzilates, compounds (18), (19), (24) and (25) were 5-10 times more active than the corresponding diphenylacetates, compounds (16), (17), (22) and (23).

Brimblecombe and Green (1968) found the pA_2 value of compound (24) to be 8.45; my result was 9.1. He also found the pA_2 value of atropine to be 8.4, which is lower than the value as stated by Schild (1947), who found the pA_2 value of atropine to be 8.77 which corresponds very closely to my result of 8.91. Brimblecombe and Green's value for compound (24) is probably low. Biel et al. (1961) found compound (18) to be slightly more active than compound (24); we found the reverse to be true. However, different testing procedures were used by Biel. Biel et al. (1962) found that compound (18) was equiactive with atropine; we found this also to be true.

2. Mydriatic Activity

The benzilates, (18), (19), (24) and (25) were 3-4 times more potent than the diphenylacetates, (16), (17), (22) and (23). No difference was seen in the mydriatic activity of the 4- and 3-piperidyl benzilates; however in the diphenylacetates the 4-analogs were slightly more active. Quaternization had little effect on potency. Again, the duration of action of these compounds was less than 24 hours.

3. Antioxotremorine Activity

All of these compounds were only feebly active. No difference in activity was observed between the two different analogs, and the results were unchanged by quaternization.

D. Anticholinergic Activity of the Miscellaneous Compounds and Standards

The results are summarized in Table XX.

1. Miscellaneous compounds.

These compounds, (105a), (105b) and (96a) were potent anticholinergics based on their pA_2 values; however they were inactive as mydriatics or antagonists of oxotremorine.

2. Standards

1. pA_2 Values

The values obtained for the standards agree with the quoted literature values.

a) Schild (1947) obtained the pA_2 value for atropine against histamine and acetylcholine and found them to be 8.77 and 5.64 respectively; my results were 8.91 and 5.91.

b) Buckett and Haining (1965) determined the pA_2 value of (+) and (-) hyoscine to be 7.29 and 9.12 respectively. My result was 8.75 obtained with the racemic

TABLE XX

ANTICHOLINERGIC, ANTIHISTAMINIC, MYDRIATIC, AND ANTIOXOTREMORINE ACTIVITY

OF MISCELLANEOUS COMPOUNDS AND STANDARDS

*No.	pA ₂ Ach	Relative ^a Potency	pA ₂ histamine	Relative ^b Potency	Mydriatic ^c Activity	Antioxotremorine activity	% decrease in tremors
105a	8.62	512.0	--	--	inactive at 0.025	0.025	inactive
105b	8.70	616.0	--	--	inactive at 0.016	0.016	inactive
96a	8.19	190.0	--	--	inactive at 0.014	0.014	inactive
A	8.91	1000.0	5.91	1000	0.0001	0.0001	25
B	8.75	691.0	5.57	1510	0.0001	0.0001	25
C	7.64	54.0	6.43	16	>0.002	0.002	50
D	7.24	21.0	6.71	3	>0.002	0.002	50
E	--	--	--	--	inactive	--	inactive

(For footnotes see following page)

*Footnotes

105a - 1,2,5-trimethyl-4-piperidyl benzilate
hydrochloride

105b - 1,2,5-trimethyl-4-piperidyl benzilate
methiodide

96a - 2- β -benzylmethyl-3- β -troylbenzilate
hydrochloride

A - atropine sulfat

B - hyoscine methiodide

C - Ethopropazine hydrochloride

D - orphenadrine hydrochloride

E - saline

a - atropine = 1000

b - atropine = 1000

c - ED₅₀ in mM/kg

mixture.

2. Mydriatic Activity

The values obtained for the standards agree with the quoted literature values. Ing et al. (1945) found atropine and hyoscine to be equiactive as mydriatics; my results agree well with this.

3. Antioxotremorine Activity

The values obtained for the standards agree with the quoted literature values. Brimblecombe et al. (1970) found that atropine and hyoscine gave very little protection against oxotremorine induced tremors. My results agree with this conclusion.

E. Cholinergic Activity of Cyclic Acetates

The results are summarized in Table XXI

The cyclic acetates, (15), (21), (59) and (65) were found to be very weakly cholinergic, but no isomer activity difference could be seen due to their weak activity. The decrease in blood pressure was blocked by hyoscine hydrobromide, therefore their effect was due to their muscarinic action.

TABLE XXI

THE MUSCARINIC POTENCY OF SOME CYCLIC PIPERIDINOLS

Compound	No.	Relative Molar Potencies (Ach=1)
N-methyl-4-piperidyl acetate methiodide	15	300
N-methyl-3-piperidyl acetate methiodide	21	660
α -1,3-dimethyl-4-piperidyl acetate methiodide	59	2000
β -1,3-dimethyl-4-piperidyl acetate methiodide	65	inactive
acetylcholine		1

DISCUSSION

From the results obtained, the structure-activity relationships can be summarized as follows:

1. The β -compounds and the tropine derivatives were more potent anticholinergics than the α -compounds or the pseudotropine derivatives. The configuration of the β -isomers and the tropine derivatives was similar to that of atropine, that is cis OCOR/NMe. In atropine it was thought that all of the activity resided in the acid moiety, and the configuration of the amino alcohol had little effect on activity (Ellenbroeck et al., 1965). In my compounds the β -isomers were 3-4 times more active than the α -isomers thus indicating the configuration of the amino alcohol was important for anticholinergic activity.

2. A hydroxyl group must be present in the esterifying acid to obtain maximal anticholinergic activity. The benzilates were 5-10 times more active than their corresponding diphenylacetates. This indicates that the hydroxyl group must have some effect on the receptor involved. Ariens and Simons (1967) stated "that potent anticholinergic agents gain a good deal of their affinity to the cholinergic receptor by the introduction of the hydroxyl group and aromatic rings in the acyl moiety, and that these moieties interact with accessory areas close

to the cholinergic receptor". Cannon and Long (1968) and Bebbington and Brimblecombe (1965) stated that the function of the hydroxyl group was probably to serve as a point of attachment on the receptor involved, through hydrogen bonding.

3. Substitution of a methyl group into the piperidine ring decreased activity. The compounds lacking a 3-methyl group were 2-5 times more active than the compounds with a 3-methyl group. The 3-methyl group therefore may hinder the attachment of the compound to the receptor in some fashion. However, the 1,2,5-trimethyl derivatives were potent anticholinergics based on their pA_2 values. These compounds were tested as pure isomers, but we were unable to determine which isomer we had obtained. Therefore these compounds may orientate themselves in such a manner that the methyl groups do not affect the binding with the receptor involved.

4. Quaternization of the nitrogen had varied effects. Quaternization of the nitrogen led to an increase in anticholinergic activity (Barlow, 1964 and Bebbington and Brimblecombe, 1965). In my compounds, the pA_2 values showed a slight decrease in potency in most compounds. In the mydriatic activity a small increase in potency was observed in most compounds. Ing et al. (1945) observed a

similar effect.

4. The 4-piperidyl derivatives were more potent than the 3-piperidyl derivatives. My results confirm the findings of Abood and Biel (1962) that the 4-piperidyl derivatives are more potent anticholinergics than the 3-piperidyl derivatives. From these results it can be said that for optimum anticholinergic activity the quaternary nitrogen must be separated from the ester function by three methylene groups. In the cholinergic receptor, however, these two functions are separated by two methylene groups. In comparing the pharmacological activity of these compounds to the standards, it can be said that these compounds were:

i) Potent antagonists of acetylcholine on the guinea pig ileum, and were very weakly antihistaminic.

ii) Potent mydriatic agents, of the same order of activity as atropine, but their duration of action (less than 24 hours) was less than that of atropine (approximately 36 hours).

iii) Weakly active as antagonists of oxotremorine.

From the results of the pharmacological evaluation of the isomers, there was a high degree of activity difference between the isomers in the PA_2 values; this activity difference decreased in the mydriatic experiments, and

was absent in the oxotremorine experiments. It may be speculated from this that 3 different anticholinergic receptors exist. However, this difference was probably due to the specificity of the tests involved and the differential distribution rate of drugs in vivo. Before any definite conclusions can be drawn more research must be done in this area.

It is also interesting to speculate whether the cholinergic and anticholinergic receptor are the same or comprise two different receptors. Brimblecombe et al. (1970a) made a comparison of the stereochemical requirements of cholinergic and anticholinergic drugs to try and answer this question. They did this by replacing the acetate function of acetylcholine by a more bulky group such as 2-cyclohexyl-2-hydroxy-2-phenacetyl, and they concluded the following:

a) Replacement of any of the N-methyl substituents in acetylcholine by other alkyl groups reduced cholinergic activity, whereas in anticholinergic compounds the N-substituent may vary over wide limits without reducing potency.

b) Formation of α -methyl acetylcholine caused a considerable reduction in muscarinic potency. Also, the muscarinic potency was dependent on the absolute configuration of the methyl substituted carbon. In anticholinergic

activity addition of a methyl group enhanced activity, and activity did not depend on the configuration of the methyl substituted carbon atom.

c) Formation of β -methyl acetylcholine (S-enantiomer) gave a compound which was equiactive with acetylcholine, whereas in the anticholinergics there was a decrease in activity.

d) Replacement of the alcoholic oxygen in acetylcholine with sulphur reduced muscarinic potency greatly; however, this had little effect on the anticholinergic potency.

From these results they stated that the stereochemical requirements for high cholinergic and high anticholinergic potency bear no resemblance, except that they are derived from one another, and it is unlikely that the two types of drugs share a common receptor. Bebbington and Brimblecombe (1965) have tried to correlate anticholinergic drugs with the cholinergic receptor, and they concluded the following:

a) The amine groups interacted at the same site as muscarinic agents.

b) The function of the hydroxyl group was less clear, but it may interact at site 3 on the cholinergic receptor. Alterations of this group affected potency

greatly.

c) Evidence concerning the effect of the ester group was conflicting.

d) Barlow et al. (1963) have shown that a polar function in the 4-position of the chain was important.

e) Phenyl groups were probably bound by van der Waals forces to an area of the receptor which was not involved in agonist interactions.

From these results it can be seen that no real correlation exists between the two receptors.

From my work a few interesting conclusions can be drawn about the receptor involved:

a) The ester function is separated from the quaternary nitrogen by three methylene groups, confirming the work of Barlow et al. (1963) that a polar function in the 4-position is necessary. This differs from the cholinergic receptor in that the ester function and the quaternary nitrogen are separated by two methylene groups.

b) A quaternary nitrogen is not required for maximal anticholinergic activity, whereas in cholinergic molecules a quaternary nitrogen is essential.

c) A hydroxyl group is most important for activity and must affect the receptor in some fashion. In the cholinergic molecules a hydroxyl group is absent.

d) Substitution of a methyl group into the piperidine ring affects the binding to the receptor in some fashion, so that a decrease in activity takes place.

My structure activity relationships tend to support the hypothesis of Brimblecombe et al. (1970a) that two receptors exist, in view of the findings that:

a) The optimum distance between the quaternary nitrogen and the ester function for maximum anticholinergic activity is three methylene groups.

b) A quaternary nitrogen is not required for potent anticholinergic activity.

c) A hydroxyl group is most important for anticholinergic activity.

EXPERIMENTAL

EXPERIMENTAL

All melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 21 and Beckmann Infrared Spectrophotometer Model 10. PMR spectra were determined on Varian Associates Models A-60 and A-60D spectrometers. Elemental analyses were performed by W. Dylke, Faculty of Pharmacy, University of Alberta. All the chemicals obtained from commercial sources were used without further purification unless otherwise specified.

I DERIVATIVES OF N-METHYL-4-PIPERIDINOL AND ITS 3-ANALOG

N-Methyl-4-Piperidyl Acetate Hydrochloride (14)

A solution of N-methyl-4-piperidinol (3.5 g, 0.028 mole), in ethyl acetate (30 ml) was added dropwise to a solution of acetyl chloride (3.1 g, 0.04 mole) in ethyl acetate (30 ml) with stirring. The solution was then heated under reflux with stirring for 24 hours. The solution was allowed to cool and the crystals which separated were collected and recrystallized from absolute alcohol-ether to give the title compound (4.9 g, 91%), m.p. 144-145°C.

IR spectrum:

ν_{\max} : 2700 cm^{-1} -2300 cm^{-1} (NH), 1730 cm^{-1} (CO)

PMR characteristics (D_2O)

2.88 δ , (NMe, singlet); 2.13 δ , (OMe, singlet); 5.1 δ (C-4 methine proton, multiplet)

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{ClNO}_2$: C, 49.64; H, 8.26; N, 7.23

Found: C, 49.71; H, 8.19; N, 7.18.

N-Methyl-4-Piperidyl Acetate Methiodide (15)

A mixture of N-methyl-4-piperidyl acetate (1.0 g, 0.006 mole) and methyl iodide (1.7 g, 0.012 mole) were dissolved in acetone (30 ml) and placed in the refrigerator for 24 hours. The crystalline solid which separated was collected and recrystallized from absolute alcohol to yield the title compound, (1.63 g, 86%) m.p. 163-165°C.

IR spectrum:

ν_{\max} : 1740 cm^{-1} (CO)

PMR characteristics (DMSO-D₆)

2.05 δ , (OMe, singlet); 3.15 δ , (NMe₂, doublet); 4.85 δ ,
(C-4 methine proton, multiplet)

Anal. Calcd. for C₉H₁₈INO₂: C, 36.15; H, 6.02; N, 4.68

Found: C, 36.23; H, 6.08; N, 4.83.

N-Methyl-3-Piperidyl Acetate Hydrochloride (20)

This was obtained by the method as described for (14).

It was recrystallized from absolute alcohol and ether to yield
the title compound (3.8 g, 79%) m.p. 143-144°C.

IR spectrum:

ν_{\max} : 1740 cm⁻¹ (CO), 2650 cm⁻¹-2350 cm⁻¹ (NH)

PMR characteristics (DMSO-D₆)

2.75 δ , (NMe, quartet); 2.06 δ , (OMe, doublet); 5.03 δ ,
(C-3 methine proton, multiplet)

Anal. Calcd. for C₈H₁₆ClNO₂: C, 49.64; H, 8.26; N, 7.23

Found: C, 49.70; H, 8.17; N, 7.45

N-Methyl-3-Piperidyl Acetate Methiodide (21)

This was obtained by the method as described for (15).

It was recrystallized from absolute alcohol to yield the title
compound (2.8 g, 80%) m.p. 165-166°C. (Biel et al., 1961,
reported 171-172°C.)

IR spectrum:

ν_{\max} : 1740 cm⁻¹ (CO)

PMR characteristics (DMSO-D₆)

2.06 δ , (OMe, singlet); 4.85 δ , (NMe₂, doublet); 5.11 δ ,
(C-3 methine proton, multiplet)

Anal. Calcd. for C₉H₁₈INO₂: C, 36.15; H, 6.02

Found: C, 35.43; H, 5.93.

N-Methyl-4-Piperidyl Diphenylacetate

N-Methyl-4-piperidinol (2.30 g, 0.02 mole) was dissolved in anhydrous benzene (20 ml) and added dropwise to a suspension of diphenylacetylchloride (0.03 moles, 6.9 g) 5 g of anhydrous sodium carbonate in 100 ml of benzene. The solution was heated under reflux for 24 hours with vigorous stirring. The sodium carbonate was filtered off and the benzene was evaporated to dryness. The resulting oil was chromatographed over alumina, and eluted with anhydrous ether. The ether was evaporated to dryness under reduced pressure to yield the crude ester (1.80 g, 29%). Coan et al. (1956) found that the oil crystallized on standing and had a m.p. of 161-162°C; ours did not crystallize. It was therefore used without any further purification.

N-Methyl-4-Piperidyl Diphenylacetate Hydrobromide (16)

1.0 g, (0.003 mole) of N-methyl-4-piperidyl diphenylacetate was dissolved in 50 ml of absolute alcohol and dry hydrogen bromide gas was passed through the solution until it was acidic. Anhydrous ether was then added until the solution

was cloudy, and then the solution was placed in the refrigerator for 48 hours. The crystals which separated were collected and recrystallized from acetone to yield the title compound, (1.1 g, 90%) m.p. 165-166°C.

IR spectrum:

ν_{\max} : 2680 cm^{-1} - 2300 cm^{-1} (NH), 1730 cm^{-1} (CO)

PMR characteristics (CDCl_3)

2.58 δ , (NMe, doublet); 5.10 δ , (C-4 methine proton, multiplet); 7.28 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{BrNO}_2$: C, 61.57; H, 6.15; N, 3.58

Found: C, 61.79; H, 6.02; N, 3.64.

N-Methyl-4-Piperidyl Diphenylacetate Methiodide (17)

This was prepared by the method as described for (15).

It was recrystallized from absolute alcohol to yield the title compound (1.3 g, 91%) m.p. 209-211°C.

IR spectrum:

ν_{\max} : 1690 cm^{-1} (CO)

PMR characteristics (DMSO-D_6)

3.2 δ (NMe_2 , doublet); 4.98 δ (C-4 methine proton, multiplet); 7.35 δ (aromatic, singlet)

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{INO}_2$: C, 55.90; H, 5.76; N, 3.58

Found: C, 55.85; H, 5.71; N, 3.13.

N-Methyl-3-Piperidyl Diphenylacetate

The transesterification procedure of Cannon (1960) was used. Methyl diphenylacetate (4.52 g, 0.02 mole) was

placed together with N-methyl-3-piperidinol (2.3 g, 0.02 mole) in a one-litre three-necked flask, equipped with a Dean-Stark moisture determination apparatus topped with a condenser and a calcium chloride tube. Dry n-heptane (600 ml) and solid sodium methoxide (0.1 g) were added to the flask and the mixture was stirred and heated under reflux. Additional sodium methoxide (0.1 g) was added after an hour reflux period. From time to time, the contents in the Dean-Stark apparatus were drained and discarded, and fresh portions of n-heptane were added to the flask to maintain the original volume. After 12 hours reflux, further sodium methoxide (0.1 g) was added. Reflux was continued for a total of 24 hours; the reaction mixture was then cooled and washed several times with water until the washings were neutral to litmus paper. The solvent was removed from the organic solution under reduced pressure in a water bath; the residue was dissolved in ether and this solution dried (Na_2SO_4), filtered, and evaporated, thus yielding the title compound (5.4 g, 84%) as an oil which was used for the further reactions without purification. (Biel et al., 1952, b.p. 173-175°C at 0.16 mm).

N-Methyl-3-Piperidyl Diphenylacetate Hydrochloride (22)

Treatment of the crude diphenylacetate (1.0 g, 0.003 mole) with an ether solution saturated with hydrogen chloride gave the title compound (0.91 g, 91%) as a solid. On recrystallization from absolute alcohol-ether it gave a m.p. 192-

193°C (Biel et al., 1952, reported 193-194°C).

IR spectrum:

ν_{\max} : 2710 cm^{-1} - 2380 cm^{-1} (NH), 1750 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

2.70 δ , (NMe, singlet); 5.20 δ , (C-3 methine proton, multiplet); 7.31 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{ClNO}_2$: C, 69.49; H, 6.90

Found: C, 69.29; H, 7.04.

N-Methyl-3-Piperidyl Diphenylacetate Methiodide (23)

The crude diphenylacetate (1.0 g, 0.003 mole) and methyl iodide (1.0 g, 0.007 mole) were dissolved in acetone (30 ml) and placed in the refrigerator for 24 hours. The solid crystalline material which separated out was collected and recrystallized from absolute alcohol to yield the title compound, (1.3 g, 91%) m.p. 95-97°C.

IR spectrum:

ν_{\max} : 1720 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

2.98 δ , (NMe₂, doublet); 5.25 δ , (C-3 methine proton, multiplet); 7.31 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{INO}_2$: C, 55.90; H, 5.76

Found: C, 55.78; H, 5.83.

N-Methyl-4-Piperidyl Benzilate

The title compound was obtained in 58% yield from N-methyl-4-piperidinol in the same manner as described for

the synthesis of N-methyl-3-piperidyl diphenylacetate, using methyl benzilate in place of methyl diphenylacetate. An oil was obtained, and it would not crystallize. (Coan et al., 1956; Klosa, 1962, reported m.p. of 162-163°C and 164°C respectively).

N-Methyl-4-Piperidyl Benzilate Hydrochloride (18)

Treatment of the crude benzilate with ether-HCl gave the title compound in 91% yield, m.p. 214-215°C from a mixture of alcohol-ether. (Biel et al., 1961, reported 213-214°C.)

IR spectrum

ν_{\max} : 3320 cm^{-1} (OH), 2750 cm^{-1} - 2410 cm^{-1} (NH),
1750 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

2.96 δ , (NMe, singlet); 4.83 δ , (C-4 methine proton, multiplet); 7.46 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{ClNO}_3$: C, 66.4; H, 6.63; N, 3.87

Found: C, 66.11; H, 6.85; N, 3.60.

N-Methyl-4-Piperidyl Benzilate Methiodide (19)

Treatment of the crude benzilate (1.0 g, 0.003 mole) with methyl iodide (1.0 g, 0.006 mole) in acetone gave the title compound (1.2 g, 92%) m.p. 198-200°C from absolute alcohol (Coan et al., 1956, reported 199-200°C).

IR spectrum:

ν_{\max} : 3390 cm^{-1} (OH), 1725 cm^{-1} (CO)

PMR characteristics (DMSO-D₆)

3.05 δ , (NMe₂, doublet); 5.11 δ , (C-4 methine proton, multiplet); 7.35 δ , (aromatic, singlet)

Anal. Calcd. for C₂₁H₂₆INO₃: C, 53.99; H, 5.56

Found: C, 53.53; H, 5.63.

N-Methyl-3-Piperidyl Benzilate

The title compound was obtained in 69% yield from N-methyl-3-piperidinol in the same manner as that described for making N-methyl-3-piperidyl diphenylacetate. An oil was obtained and it was used for further reactions without purification (Biel et al., 1955, reported b.p. 198-199°C at 0.20 mm).

N-Methyl-3-Piperidyl Benzilate Hydrochloride (24)

Treatment of the crude benzilate (1.0 g, 0.003 mole) with ether-HCl gave the title compound in 91% yield, m.p. 217-218°C from acetone (Biel et al., 1955, reported 221-223°C).

IR spectrum:

ν_{max} : 3400 cm⁻¹ (OH), 2710 cm⁻¹ - 2400 cm⁻¹ (NH),
1750 cm⁻¹ (CO)

PMR characteristics (DMSO-D₆)

2.58 δ , (NMe, singlet); 5.13 δ , (C-3 methine proton, multiplet); 7.23 δ , (aromatic, singlet)

Anal. Calcd. for C₂₀H₂₄ClNO₃: C, 66.4; H, 6.6

Found: C, 66.45; H, 6.46.

N-Methyl-3-Piperidyl Benzilate Methiodide (25)

Treatment of the crude benzilate (1.0 g, 0.003 mole) with methyl iodide (1.0 g, 0.007 mole) in acetone gave the title compound (1.3 g, 97%) m.p. 221-223°C from absolute alcohol.

IR spectrum:

ν_{max} : 3420 cm^{-1} (OH), 1730 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

4.61 δ , (NMe_2 , doublet); 5.28 δ , (C-3 methine proton, multiplet); 7.30 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{INO}_3$: C, 53.99; H, 5.56

Found: C, 54.12; H, 5.57.

Diphenylacetyl Chloride (26a)

A mixture of diphenylacetic acid (20 g, 0.094 mole) and purified thionyl chloride (23.8 g, 0.2 mole) was refluxed for 10 hours, and the excess of thionyl chloride was taken off under reduced pressure, thus affording an oil of (26a) (20 g, 92%). The oil was dissolved in boiling ligroin and upon cooling yielded a white crystalline solid m.p. 56-57°C (56-57°C, Merck Index, 1968).

Methyl Diphenylacetate (27)

A mixture of diphenylacetic acid (21.2 g, 0.1 mole), methanol (10 g, 0.3 mole), sulfuric acid (15 ml) and methylene chloride (100 ml) was heated under reflux for 24 hours.

The reaction mixture was cooled and diluted with 100 ml of water. The organic layer was separated and washed with sodium carbonate solution (10%) until neutral and evaporated under reduced pressure to yield the title compound (22.6 g, 84%) m.p. 61°C from ligroin (Merck Index, 1968, m.p. 58°C).

II SYNTHESIS OF 1,3-DIMETHYL-4-PIPERIDONE

(β -Carbomethoxy-N-Propyl)-Methylamine (36)

A solution of methyl methacrylate (302 g, 3 mole) in absolute ethanol (200 g) was added with stirring to a cooled solution of methylamine (62 g, 2 mole) in absolute ethanol (225 g) over a period of three hours. The product after standing in the dark for a period of three days at room temperature, was fractionally distilled under reduced pressure to give the title compound (132.2 g, 50%) as a colorless mobile oil, b.p. 65-68°C at 20 mm, N_D^{20} 1.4138 (Kirk, 1958, reported b.p. 66-68°C at 20 mm, N_D^{20} 1.4238; Howton, 1945, reported 48.8-49.5 at 8 mm).

(β -Carbomethoxy-N-Propyl)-(β -Carbomethoxy-ethyl)-Methylamine (37)

A mixture of (36) (132 g, 1.0 mole) and methyl acrylate (88.0 g, 1.0 mole) was left 5 days in the dark at room temperature. The resulting amber colored liquid was fractionally distilled under reduced pressure to give the title compound (183 g, 85%) as a colorless oil, b.p. 110-112°C at 4.0 mm, N_D^{20} 1.45327 (Kirk, 1958, reported b.p. 110-115°C at 4.0 mm, N_D^{20} 1.4539; Howton, 1945, reported 105-107°C at 4.0 mm).

1,3-Dimethyl-4-Piperidone (39)

87 g, (0.4 mole) of (37) was added dropwise to a stirred suspension of bird shot sodium (9.2 g, 0.4 mole) in xylene (200 ml) heated in an oil bath at 60°C. When the initial

reaction had subsided, the mixture, protected from moisture by a calcium chloride tube, was refluxed for three hours, by which time all the sodium had disappeared. The resulting dark liquid was cooled and added with stirring to ice water (200 ml). The aqueous layer was separated, washed with ether (2 X 100 ml) and acidified with concentrated hydrochloric acid. One drop of this solution gave a blood red color with ferric chloride solution. After refluxing for four hours the initial vigorous evolution of carbon dioxide became negligible and a negative result was obtained with ferric chloride solution. The product was evaporated to small bulk under reduced pressure, the residue was made alkaline with solid potassium hydroxide, and extracted with chloroform in a continuous extractor for 48 hours. The chloroform was dried (Na_2SO_4) and evaporated under reduced pressure to small bulk and then fractionally distilled under reduced pressure to give the title compound (19 g, 39%) as a colorless mobile oil, b.p. $79-81^\circ\text{C}$ at 20 mm, n_{D}^{20} 1.4517 (Kirk, 1958, reported $76-78^\circ\text{C}$ at 20 mm, n_{D}^{20} 1.4510; Howton, 1945, reported b.p. $43-43.5^\circ\text{C}$ at 5.5 mm).

III REDUCTION OF 1,3-DIMETHYL-4-PIPERIDONE BY VARIOUS
METHODS TO YIELD THE ISOMERIC 1,3-DIMETHYL-4-
PIPERIDINOL (29)

Lithium Aluminium Hydride

A suspension of lithium aluminium hydride (8.0 g, 0.2 mole) in dry ether (75 ml) was stirred vigorously for 15 minutes. To the resulting slurry a solution of 1,3-dimethyl-4-piperidone (25.4 g, 0.2 mole) in dry ether (75 ml) was added dropwise fast enough just to keep the solution refluxing. The solution, protected from moisture by a calcium chloride tube, was heated under reflux for a further 8 hours, with stirring. The reaction mixture was cooled and decomposed carefully with ice water. The ether layer was decanted and dried (Na_2SO_4) and evaporated to dryness to yield the crude title compound as a viscous oil (21.5 g, 84%). It had a boiling point of 78.0 at 1 mm (Ganellin and Spickett, 1965, found b.p. 64.0 at 0.25 mm). It was used without further purification.

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH), C=O band was absent.

Aluminium Isopropoxide

1,3-Dimethyl-4-piperidone (10.0 g, 0.078 mole) in isopropanol (180 ml) was added to a solution of aluminium isopropoxide (16.0 g, 0.078 mole) in isopropanol (100 ml) kept in a 500 ml flask fitted with a Vigreux column and a

condenser. Refluxing and testing for acetone with 2,4—dinitrophenylhydrazine were carried out as described in the literature (Welds, 1947). After a negative test for acetone was obtained for 2-3 hours (total reaction time 9 hours), most of the excess isopropanol was removed by distillation and the residue was hydrolyzed with ice cold 50% ammonium hydroxide solution and extracted with ether on a continuous extraction apparatus. The ether was dried (Na_2SO_4) and evaporated to dryness under reduced pressure to yield the crude title product (10.0 g, 98%) as a thick viscous oil. It was used for further reaction without purification.

IR spectrum:

ν_{max} : very broad OH at 3400 cm^{-1} ; $\nu_{\text{C=O}}$ band was absent.

Adams Catalyst (Platinum oxide)

1,3—Dimethyl-4-piperidone (1.0 g, 0.008 mole) was dissolved in absolute ethanol (100 ml) and to it was added 150 mg of platinum oxide in 50 ml of absolute ethanol. Hydrogenation was carried out at room temperature and pressure. After the theoretical amount of hydrogen was taken up the catalyst was filtered off and the ethanol evaporated under reduced pressure to yield 1.0 g (100%) of the crude title compound as a thick viscous oil. It was used for further reactions without further purification.

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH); $\nu_{\text{C=O}}$ band was absent.

Palladium Charcoal

The above was repeated using palladium charcoal (10%) in place of platinum oxide. The reduction did not take place.

α -(trans)-1,3-Dimethyl-4-Piperidinol Hydrochloride (47)

The crude 1,3-dimethyl-4-piperidinol (4.3 g, 0.033 mole) obtained from the lithium aluminium hydride reaction was dissolved in absolute ethanol (50 ml) and dry hydrogen chloride gas was passed through it until it was acidic to litmus. Anhydrous ether was then added to it until the solution became cloudy. It was allowed to crystallize at room temperature. A fraction of (27 g, 63%) crystals were obtained after recrystallization from alcohol-ether, which had a m.p. of 184-186 °C (Mistryukov, 1965, reported 183°C - 184°C).

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH), 2700-2310 cm^{-1} (NH)

PMR characteristics (DMSO- D_6)

0.95 δ , (2° methyl, doublet); 2.68 δ , (NMe, singlet)

Anal. Calcd. for $\text{C}_7\text{H}_{16}\text{ClNO}$: C, 50.79; H, 9.66; N, 8.45

Found: C, 50.74; H, 9.88; N, 8.70.

From the mother liquor no other fraction of crystals was obtained.

β -(cis)-1,3-Dimethyl-4-Piperidyl Acetate Hydrochloride (64)

From the mother liquors from (47) the free base of

1,3-dimethyl-4-piperidinol was liberated by treatment with ammonium hydroxide and extraction with ether. The ether was dried (Na_2SO_4) and evaporated to dryness to yield the crude alcohol (28). A sample of this 1,3-dimethyl-4-piperidinol (2.0 g, 0.015 mole) was dissolved in ethyl acetate (75 ml) and added dropwise to a solution of acetyl chloride (3.1 g, 0.04 mole) in ethyl acetate (30 ml) with stirring. The solution, protected from moisture by a calcium chloride drying tube, was heated under reflux for 24 hours. The solution was cooled and a crystalline solid subsequently crystallized in 24 hours when placed in the refrigerator. The solid was recrystallized from alcohol ether to yield the title compound (2.7 g, 90%), m.p. 145-146°C.

IR spectrum:

ν_{max} : 2740-2310 cm^{-1} (NH), 1740 cm^{-1} (CO)

PMR characteristics ($\text{DMSO}-d_6$)

2.70 δ , (NMe, singlet); 2.06 δ , (OMe, singlet); 4.93 δ , (C-4 methine proton, multiplet, base width 17 Hz, therefore equatorial proton)

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{ClNO}_2$: C, 52.07; H, 8.67; N, 6.74

Found: C, 51.93; H, 8.31; N, 7.05.

α -(trans)-1,3-Dimethyl-4-Piperidyl Acetate Hydrochloride (58)

The pure α -hydrochloride (47) (2 g) was neutralized with dilute ammonia and extracted with ether. The extract was dried (Na_2SO_4), the solvent evaporated to leave the crude

free base alcohol (1.5 g,) of α -1,3-dimethyl-4-piperidinol.

The alcohol was acetylated by the same procedure as for (64). Its m.p. 208-210 °C from alcohol-ether (2.2g, 92%).

IR spectrum:

ν_{max} : 2700-2390 cm^{-1} (NH), 1739 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

2.68 δ , (NMe, singlet); 2.06 δ , (OMe, singlet); 4.61 δ , (C-4 methine proton, multiplet, base width 24 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{ClNO}_2$: C, 52.07; H, 8.67; N, 6.74

Found: C, 52.24; H, 8.90; N, 6.95.

β -1,3-Dimethyl-4-Piperidinol Hydrochloride (48)

The pure β -ester hydrochloride (64) (5.0 g) was neutralized with dilute ammonia and extracted with ether. The extract was dried (Na_2SO_4), the solvent evaporated to leave the crude free base (4.0 g) of 1,3-dimethyl-4-piperidyl acetate.

A suspension of lithium aluminium hydride (1.0 g, 0.025 mole) in dry ether (75 ml) was stirred vigorously for 15 minutes. To the resulting slurry a solution of β -1,3-dimethyl-4-piperidyl acetate (4.0 g, 0.023 mole) was added dropwise just fast enough to keep the solution refluxing. The solution, protected from moisture by a calcium chloride drying tube, was heated under reflux for a further 8 hours. The reaction mixture was then cooled and decomposed carefully with ice water. The ether layer was decanted and dried (Na_2SO_4)

and evaporated to dryness under reduced pressure to yield the crude β -1,3-dimethyl-4-piperidinol (2.4 g, 84%) as a thick viscous oil.

Treatment of the crude oil with ether-HCl gave the title compound (2.8 g, 90.0%) from alcohol-ether after two weeks, m.p. 110-111°C.

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH); $\nu_{\text{C=O}}$ band absent

PMR characteristics (CDCl_3)

0.90 δ , (secondary Me); 2.65 δ , (NMe, singlet)

Anal. Calcd. for $\text{C}_7\text{H}_{16}\text{ClNO}$: C, 50.79; H, 9.66; N, 8.45

Found: C, 50.71; H, 9.64; N, 8.13.

IV PROCEDURE ADOPTED FOR SEPARATION OF ISOMERS

A solution of the diastereoisomeric 1,3-dimethyl-4-piperidinols (5.0 g, 0.04 mole) obtained from the lithium aluminium hydride reduction of the ketone in ethyl acetate (30 ml) was added dropwise to a solution of acetyl chloride (6.4 g, 0.08 mole) in ethyl acetate 150 ml with stirring. The solution, protected from moisture by a calcium chloride drying tube, was heated under reflux for 24 hours. The solution was allowed to cool and the solid which precipitated (5.8 g, 70%) was collected and recrystallized from alcohol-ether to yield 5.8 g α -1,3-dimethyl-4-piperidyl acetate hydrochloride, m.p. 208-210 °C.

The α -ester hydrochloride (5.8 g) was neutralized with dilute ammonia and extracted with ether. The extract was dried (Na_2SO_4), the solvent evaporated under reduced pressure to leave the crude free base (5.0 g, 100%) α -1,3-dimethyl-4-piperidyl acetate.

This base 5.0 g (0.03 mole) was dissolved in 75 ml of dry ether and added to a stirred suspension of lithium aluminium hydride (1.2 g, 0.03 mole) just fast enough to keep the solution refluxing. The solution, protected from moisture by a calcium chloride drying tube, was heated under reflux for 5 hours. The reaction mixture was then cooled and decomposed carefully with ice cold water. The ether layer was then decanted, dried (Na_2SO_4), and evaporated to dryness to yield 3.6 g (97%) of α -1,3-dimethyl-4-piperidinol. It was used for further reactions without any purification.

The mother liquor from the acetylation procedure was placed in the refrigerator and in 48 hours yielded 2.5 g of the β -1,3-dimethyl-4-piperidyl acetate hydrochloride, m.p. 143-145°C. This was treated in the same manner as the α -isomer, to yield 1.6 g of the β -1,3-dimethyl-4-piperidinol.

This procedure was used for the separation of isomers from all reduction procedures.

V N-BENZYL-3-METHYL-4-PIPERIDINOL (51)

A suspension of lithium aluminium hydride (3.8 g, 0.1 mole) in dry ether (200 ml) was stirred vigorously for 15

minutes. To the resulting slurry a solution of N-benzyl-3-methyl-4-piperidone (20.3 g, 0.1 mole) in dry ether (200 ml) was added dropwise, just fast enough to keep the reaction refluxing. The solution, protected from moisture by a calcium chloride drying tube, was refluxed for 8 hours. The reaction mixture was cooled and decomposed carefully with ice water. The ether was decanted, dried (Na_2SO_4) and evaporated to dryness under reduced pressure to yield the crude alcohol, (19 g, 92%).

IR spectrum:

ν_{max} : 3450 cm^{-1} (very broad OH); $\nu_{\text{C=O}}$ band absent.

All attempts at making a salt were unsuccessful.

VI SEPARATION OF ISOMERS OF N-BENZYL-3-METHYL-4-PIPERIDINOL

A solution of N-benzyl-3-methyl-4-piperidinol obtained from the lithium aluminium hydride reduction (3.0 g, 0.014 mole), in ethyl acetate (20 ml) was added dropwise to a solution of acetyl chloride (2.0 g, 0.025 mole) and ethyl acetate (20 ml). The solution, protected from moisture by a calcium chloride drying tube, was refluxed for 8 hours. The solution was then cooled and the precipitate which formed was collected (1.0 g) and recrystallized from alcohol-ether to yield the α -isomer (identified by PMR), m.p. 255-256 °C. Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{ClNO}_2$: C, 63.49; H, 7.81; N, 4.94 Found: C, 63.83; H, 7.79; N, 4.95.

The mother liquor was placed in the refrigerator and a solid (1.83 g, 0.0064 mole) was obtained.

It was recrystallized from alcohol-ether to yield the β -isomer (identified by PMR), m.p. 180-182°C.

Anal. Calcd. for: $C_{15}H_{22}ClNO_2$: C, 63.49; H, 7.81; N, 4.94

Found: C, 63.25; H, 7.65; N, 5.09

β -N-Benzyl-3-Methyl-4-Piperidinol (53)

The β -ester hydrochloride (5.60 g) was neutralized with dilute ammonia and extracted with ether. The extract was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to leave the crude free base (4.8 g), β -N-benzyl-3-methyl-4-piperidyl acetate.

This was dissolved in 35 ml of dry ether and added dropwise to a stirred suspension of lithium aluminium hydride (0.8 g, 0.02 mole) in 75 ml of dry ether just fast enough to keep it refluxing. The solution, protected from moisture by a calcium chloride drying tube, was heated under reflux for 8 hours. The reaction mixture was then cooled and decomposed carefully with ice water. The ether layer was decanted, dried (Na_2SO_4), and evaporated to dryness under reduced pressure to yield the crude β -alcohol (53) (3.9 g) as a viscous oil.

IR spectrum:

ν_{max} : 3300 cm^{-1} (very broad OH); $\nu_{C=O}$ band absent.

β -3-Methyl-4-Piperidinol (54)

To 3.9 g of (53) dissolved in absolute alcohol (50 ml) was added 390 mg of palladium (10%) on charcoal suspended in absolute alcohol (25 ml). Hydrogenation was carried out at room temperature and pressure. After the theoretical yield of hydrogen was taken up, the catalyst was filtered off and the ethanol evaporated under reduced pressure to yield (1.9 g) of the title compound as a colorless oil.

β -1,3-Dimethyl-4-Piperidinol Hydrochloride (48)

A solution of 1.9 g of (54), formaldehyde (5.0 g), formic acid, (5.0 g) in ethanol (100 ml) was heated under reflux for 24 hours. The solution was cooled and evaporated to dryness under reduced pressure. The excess of water was azeotroped off with benzene. The resulting oil was then dissolved in dry ether and dried (Na_2SO_4). The ether was then evaporated off under reduced pressure leaving 2.0 g of the title compound as a viscous oil. The crude alcohol was then treated with ether-HCl to yield the title compound, (2.2 g), which was recrystallized with difficulty from alcohol-ether. The m.p., 109-111°C, was identical with the sample prepared by the previous procedure. A mixed melting point of the two compounds produced no decrease in melting point.

VII SYNTHESIS OF METHIODIDES OF ESTERS OF α - AND β -

1,3-DIMETHYL-4-PIPERIDINOL.

α -1,3-Dimethyl-4-Piperidyl Acetate Methiodide (59)

The α -ester hydrochloride (3.5 g) (58) was neutralized with dilute ammonia and extracted with ether. The extract was dried (Na_2SO_4); the solvent evaporated under reduced pressure to leave the crude free base (2.8 g) of α -1,3-dimethyl-4-piperidyl acetate.

The basic ester (1.0 g, 0.006 mole) was mixed with methyl iodide (2.8 g, 0.02 mole) in acetone (30 ml) and the mixture was left in the refrigerator overnight. The crystalline solid which precipitated was collected and recrystallized from absolute ethanol to yield (2.0 g, 94%) of the α -1,3-dimethyl-4-piperidyl acetate methiodide, m.p. 192-193°C.

IR spectrum:

ν_{max} : 1735 cm^{-1} (CO)

PMR characteristics (DMSO-D_6)

3.13 δ , (NMe_2 , singlet); 4.61 δ , (C-4 methine proton, multiplet, base width 34 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{INO}_2$: C, 38.37; H, 6.38; N, 4.47

Found: C, 38.37; H, 6.43; N, 4.14.

β -1,3-Dimethyl-4-Piperidyl Acetate Methiodide (65)

The procedure employed to make the α^* -(trans) isomer (59) was used to prepare the title compound. The crude β -1,3-dimethyl-4-piperidyl acetate (1.0 g, 0.006 mole) yielded

the title compound (1.8 g, 86%) as a white crystalline solid, m.p. 184-185°C, from absolute alcohol.

IR spectrum:

ν_{\max} : 1745 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

3.20 δ , (NMe_2 , doublet); 4.85 δ , (C-4 methine proton, multiplet, base width 13.0 Hz, therefore equatorial proton)

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{INO}_2$: C, 38.37; H, 6.38

Found: C, 38.26; H, 6.41.

α -1,3-Dimethyl-4-Piperidyl Diphenylacetate Hydrochloride (60)

The method used for the synthesis of N-methyl-3-piperidyl diphenylacetate was used. The crude α -1,3-dimethyl-4-piperidinol (1.6 g, 0.012 mole) yielded the crude ester (1.4 g, 34%). The crude ester was then treated with ether-HCl to yield the title compound (1.6 g, 90.0%), m.p. 122-124°C.

IR spectrum:

ν_{\max} : 1740 cm^{-1} (CO), 1610 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

2.66 δ , (NMe , singlet); 4.68 δ , (C-4 methine proton, multiplet, base width 31 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{ClNO}_2$: C, 70.12; H, 7.22; N, 3.89

Found: C, 69.98; H, 7.25; N, 3.98.

α -1,3-Dimethyl-4-Piperidyl Diphenylacetate Methiodide (61)

The crude free base (2.0 g, 0.006 mole) obtained from

(60) was placed with methyl iodide (1.6 g, 0.012 mole) in acetone (30 ml) and this solution was placed in the refrigerator for 24 hours. The crystals which formed were collected to yield the title compound (2.4 g, 85%) from absolute alcohol, m.p. 243-245°C.

IR spectrum:

ν_{\max} : 1735 cm^{-1} (CO), 1625 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

3.13 δ , (NMe_2 , singlet); 4.70 δ , (C-4 methine proton, multiplet, base width 31 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{INO}_2$: C, 56.80; H, 6.01

Found: C, 57.19; H, 6.15.

β -1,3-Dimethyl-4-Piperidyl Diphenylacetate Hydrobromide (66)

The procedure employed to make the N-methyl-4-piperidyl diphenylacetate was used to prepare the title compound. The crude β -1,3-dimethyl-4-piperidinol (1.5 g, 0.012 mole) yielded the title compound (1.4 g, 34%) as the crude free base ester. The crude free base was then treated with ether-HBr to yield the title compound (1.6 g, 90%) as a white crystalline solid from alcohol-ether, m.p. 202-204°C.

IR spectrum:

ν_{\max} : 1730 cm^{-1} (CO), 1640 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

2.76 δ , (NMe , singlet); 5.00 δ , (C-4 methine proton, multiplet; base width 13 Hz, therefore equatorial proton)

Anal. Calcd. for $C_{21}H_{26}BrNO_2$: C, 62.40; H, 6.43

Found: C, 62.71; H, 6.43.

β -1,3-Dimethyl-4-Piperidyl Diphenylacetate Methiodide (67)

The crude free base ester obtained from (6), (1.45 g, 0.0045 mole), was placed with methyl iodide (1.6 g, 0.012 mole) in acetone (30 ml) and this solution was placed in the refrigerator for 24 hours. The resulting crystals were collected and recrystallized from absolute alcohol to yield the title compound (1.9 g, 89.0%), m.p. 187-188°C.

IR spectrum:

ν_{\max} : 1740 cm^{-1} (CO), 1635 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

2.61 δ , (NMe_2 , doublet); 4.95 δ , (C-4 methine proton, multiplet; base width 13.5 Hz, therefore equatorial proton)

Anal. Calcd. for $C_{22}H_{28}INO_2$: C, 56.80; H, 6.01

Found: C, 57.10; H, 6.00.

α -1,3-Dimethyl-4-Piperidyl Benzilate Hydrochloride (62)

The procedure employed to make N-methyl-4-piperidyl benzilate was used to prepare the free base. Crude α -1,3-dimethyl-4-piperidinol (5.1 g, 0.04 mole) yielded the free base ester (4.5 g, 34.0%). The free base ester (2.0 g, 0.006 mole) was treated with ether-HCl to yield the title compound (2.7 g, 97%) from alcohol-ether, m.p. 183-184°C.

IR spectrum:

ν_{\max} : 1710 cm^{-1} (CO), 1640 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

2.61 δ , (NMe, singlet); 4.66 δ , (C-4 methine proton, multiplet; base width 31 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{ClNO}_3$: C, 67.16; H, 6.92; N, 3.92

Found: C, 66.86; H, 7.08; N, 3.56

α -1,3-Dimethyl-4-Piperidyl Benzilate Methiodide (63)

The crude free base ester obtained from (62) (2.0 g, 0.006 mole) was placed with methyl iodide (1.6 g, 0.012 mole) in acetone (30 ml) and the solution placed in the refrigerator for 24 hours. The resulting crystals were collected and recrystallized from absolute alcohol to yield the title compound (2.7 g, 93%) as a white crystalline solid, m.p. 209-211°C.

IR spectrum:

ν_{\max} : 1730 cm^{-1} (CO), 1640 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

3.11 δ , (NMe_2 , doublet); 4.68 δ , (C-4 methine proton, multiplet, base width 28 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{INO}_3$: C, 54.79; H, 5.81

Found: C, 55.27; H, 6.09.

β -1,3-Dimethyl-4-Piperidyl Benzilate Hydrochloride (68)

The procedure employed to make the α -isomer was used

to prepare the free base of the ester. Crude β -1,3-dimethyl-4-piperidinol (4.9 g, 0.04 mole) yielded the ester free base (3.2 g, 24%) as a crude viscous oil. The free base (2.0 g, 0.006 mole) was treated with ether-HCl to yield the title compound (2.2 g, 95%) as a white crystalline solid, m.p. 266-267°C.

IR spectrum:

ν_{\max} : 1740 cm^{-1} (CO), 2710 cm^{-1} - 2440 cm^{-1} (NH)

PMR characteristics (DMSO- D_6)

2.73 δ , (NMe, singlet); 5.03 δ , (C-4 methine proton, multiplet; base width 13.0 Hz, therefore equatorial proton)

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{ClNO}_3$: C, 67.16; H, 6.92

Found: C, 67.06; H, 7.01.

β -1,3-Dimethyl-4-Piperidyl Benzilate Methiodide (69).

The crude ester free base (1.2 g, 0.0035 mole) was treated with methyl iodide (2.0 g, 0.014 mole) in acetone (30 ml) and the solution was placed in the refrigerator for 24 hours. The resulting solid was collected and recrystallized from absolute alcohol to yield the title compound (1.5 g, 93%) as a white crystalline solid, m.p. 189-190°C.

IR spectrum:

ν_{\max} : 1740 cm^{-1} (CO), 1640 cm^{-1} (C=C)

PMR characteristics (DMSO- D_6)

3.10 δ , (NMe_2 , doublet); 5.01 δ , (C-4 methine proton, multiplet, base width 15.0 Hz, therefore equatorial proton)

Anal. Calcd. for $C_{22}H_{28}INO_3$: C, 54.97; H, 5.81; N, 2.90
Found: C, 54.88; H, 5.82; N, 2.86.

VIII METHIODIDE OF ALCOHOLS

α -1,3-Dimethyl-4-Piperidinol Methiodide (78)

Treatment of the crude α -alcohol (1.0 g, 0.008 mole) with methyl iodide (1.6 g, 0.0120 mole) in acetone (30 ml) yielded the title compound (2.0 g, 92%), m.p. 161-163°C from absolute alcohol.

IR spectrum:

ν_{\max} : 3400 cm^{-1} (very broad OH)

PMR characteristics (DMSO- D_6)

4.96 δ , (OH, doublet); 3.16 δ , (NMe₂, doublet)

Anal. Calcd. for $C_8H_{18}INO$: C, 35.45; H, 6.64; N, 5.16

Found: C, 35.60; H, 6.86; N, 5.05.

β -1,3-Dimethyl-4-Piperidinol Methiodide (79)

Treatment of the crude β -alcohol (1.0 g, 0.008 mole) with methyl iodide (1.6 g, 0.012 mole) in acetone (30 ml) yielded the title compound (2.1 g, 94%), m.p. 208-210°C from absolute alcohol.

IR spectrum:

ν_{\max} : 3400 cm^{-1} (very broad OH)

PMR characteristics (DMSO- D_6)

4.93 δ , (OH, doublet); 3.18 δ , (NMe₂, doublet)

Anal. Calcd. for $C_8H_{18}INO$: C, 35.45; H, 6.64; N, 5.16
Found: C, 35.48; H, 6.77; N, 5.41.

N-Methyl-4-Piperidinol Methiodide (80)

Treatment of the alcohol, (1.0 g, 0.008 mole) with methyl iodide (3.2 g, 0.024 mole) in acetone (30 ml) yielded the title compound (1.9g, 88%), m.p. greater than $320^{\circ}C$, from absolute alcohol.

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH)

PMR characteristics (DMSO- D_6)

4.83 δ , (OH, doublet); 3.21 δ , (NMe₂, doublet)

Anal. Calcd. for $C_7H_{16}INO$: C, 32.71; H, 6.22; N, 5.44
Found: C, 32.74; H, 5.99; N, 5.39.

N-Methyl-3-Piperidinol Methiodide (81)

Treatment of the alcohol (1.2 g, 0.01 mole) with methyl iodide (5.6 g, 0.04 mole) in acetone (30 ml) yielded the title compound (2.4 g, 93%), m.p. $317^{\circ}C$ from absolute alcohol.

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH)

PMR characteristics (DMSO- D_6)

5.30 δ , (OH, doublet); 3.18 δ , (NMe₂, doublet)

Anal. Calcd. for $C_7H_{16}INO$: C, 32.71; H, 6.22
Found: C, 32.78; H, 6.19.

IX SYNTHESIS OF TROPINE AND PSEUDOTROPINE DERIVATIVES

Tropine Methiodide (95)

Treatment of tropine (1.0 g, 0.007 mole) with methyl iodide (1.6 g, 0.012 mole) in acetone (30 ml) yielded the title compound (1.7 g, 88%), m.p. $>330^{\circ}\text{C}$ from alcohol (Guermek, L. and Nador, K., 1953, found $>315^{\circ}\text{C}$).

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH)

PMR characteristics (DMSO- D_6)

3.03 δ , (NMe_2 , doublet); 4.85 δ , (OH, doublet)

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{INO}$: C, 38.19; H, 6.39; N, 4.94

Found: C, 38.49; H, 6.17; N, 4.92.

Pseudotropine Methiodide (95a)

Treatment of pseudotropine (1.0 g, 0.007 mole) with methyl iodide (1.6 g, 0.012 mole) in acetone (30 ml) yielded the title compound (1.8 g, 98%), m.p. $>330^{\circ}\text{C}$ from alcohol.

IR spectrum:

ν_{max} : 3400 cm^{-1} (very broad OH)

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{INO}$: C, 38.19; H, 6.39; N, 4.94

Found: C, 38.21; H, 6.19; N, 4.92.

Tropyl Acetate Hydrochloride

A solution of tropine (100 mg, 0.0007 mole) in ethyl acetate (10 ml) was added dropwise to a stirred solution of acetyl chloride (0.8 g, 0.01 mole) in ethyl acetate (20 ml). The solution, protected from moisture by a calcium

chloride drying tube, was heated under reflux for 8 hours. The solution was allowed to cool and anhydrous ether was added to facilitate precipitation. The solid which separated was collected and recrystallized from absolute alcohol-ether to yield the title compound (1.4 g, 91%), m.p. 209-210 °C.

IR spectrum:

ν_{\max} : 2700 cm^{-1} - 2310 cm^{-1} (NH); 1710 cm^{-1} (CO)

PMR characteristics (D_2O)

2.13 δ , (OMe, singlet); 2.80 δ , (NMe, singlet)

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{ClNO}_2$: C, 54.95; H, 8.23

Found: C, 54.60; H, 8.25.

Pseudotropyl Acetate Hydrochloride

This compound was prepared in 86% yield by the same procedure as for tropyl acetate; m.p. 218-219°C from absolute alcohol.

IR spectrum:

ν_{\max} : 2700 cm^{-1} - 2310 cm^{-1} (NH), 1740 cm^{-1} (CO)

PMR characteristics (D_2O)

2.13 δ , (OMe, singlet); 2.76 δ , (NMe, singlet)

Anal. Calcd. for $\text{C}_{10}\text{H}_{28}\text{ClNO}_2$: C, 54.95; H, 8.23; N, 6.40

Found: C, 54.95; H, 8.24; N, 6.57.

Tropine Benzilate

The transesterification procedure of Cannon (1960) was used, as explained earlier, to yield the title compound

(5.2 g, 68%), m.p. 146-148°C from benzene (Hromatka et al., 1952, reported 152-153°C).

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.22, H, 7.11, N, 3.99

Found: C, 75.01; H, 6.96; N, 4.02.

Tropine Benzilate Hydrochloride

Treatment of the benzilate with ether HCl gave the title compound in 98% yield, m.p. 242-243°C from alcohol-ether (Hromatka et al., 1952, reported 239-240°C).

IR spectrum:

ν_{\max} : 1720 cm^{-1} (CO), 2810 cm^{-1} - 2700 cm^{-1} (NH)

PMR characteristics (DMSO- D_6)

2.60 δ , (NMe, singlet); 6.73 δ , (OH, singlet);

7.40 δ , (aromatic, singlet)

Anal. Calcd. for $C_{22}H_{26}ClNO_3$: C, 68.15; H, 6.70; N, 3.61

Found: C, 67.95; H, 6.69; N, 3.84.

Tropine Benzilate Methiodide

Treatment of the benzilate with an excess of methyl iodide in acetone yielded the title compound in 99% yield, m.p. 278°C, from alcohol-ether.

IR spectrum:

ν_{\max} : 3490 cm^{-1} (OH), 2740 cm^{-1} - 2310 cm^{-1} (NH),
1720 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

2.93 δ , (NMe₂, doublet), 6.68 δ , (OH, singlet),

7.38 δ , (aromatic, singlet)

Anal. Calcd. for $C_{23}H_{28}INO_3$: C, 56.02; H, 5.67

Found: C, 56.29; H, 5.54.

Pseudotropine Benzilate

The title compound was obtained in 53% yield from pseudotropine in the same manner as described for tropine benzilate. The crystalline material had a m.p. 156-157°C, from acetone.

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.22; H, 7.11

Found: C, 75.60; H, 7.11.

Pseudotropine Benzilate Hydrochloride

Treatment of the benzilate with ether-HCl gave the title compound in 99% yield, m.p. 226-228°C, from alcohol-ether (Kreitmar, 1936, reported 232°C).

IR spectrum:

ν_{\max} : 1720 cm^{-1} (CO), 2840 cm^{-1} - 2330 cm^{-1} (NH)

PMR characteristics (D_2O)

2.90 δ , (NMe, singlet); 6.73 δ , (OH, singlet);

7.51 δ , (aromatic, singlet)

Anal. Calcd. for $C_{22}H_{26}ClNO_3$: C, 68.15; H, 6.70; N, 3.61

Found: C, 67.87; H, 6.56; N, 3.60.

Pseudotropine Benzilate Methiodide

Treatment of the benzilate with an excess of methyl iodide in acetone gave the title compound in 92% yield, m.p. 246-247°C.

IR spectrum:

ν_{max} : 1730 cm^{-1} (CO), 2710 cm^{-1} - 2400 cm^{-1} (NH)

PMR characteristics (DMSO- D_6)

3.13 δ , (NMe_2 , doublet); 6.58 δ , (OH, singlet);

7.38 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{23}\text{H}_{28}\text{INO}_3$: C, 56.02; H, 5.67

Found: C, 56.25; H, 5.77.

X SYNTHESIS OF COCAINE DERIVATIVES

2- β -Hydroxymethyl-3- β -Tropanol (97)

Cocaine (3.0 g, 0.01 mole) in ether (75 ml) was added to a stirred suspension of lithium aluminium hydride (1.0 g, 0.025 mole) in ether (75 ml) just fast enough to keep the reaction refluxing. The solution, protected from moisture by a calcium chloride drying tube, was heated under reflux for 8 hours. The solution was cooled and decomposed with ice water. The ether layer was then decanted, dried (Na_2SO_4), and evaporated to dryness to yield the title compound (1.5 g, 75%).

2- β -Hydroxymethyl-3- β -Tropanol Hydrochloride (97a)

The free base (97) was treated with ether-HCl to yield the title compound in 98% yield, m.p. 276°C, from alcohol-ether (Kovacs et al., 1954, reported 268-270°C).

IR spectrum:

ν_{\max} : 3350 cm^{-1} (OH), 2700 cm^{-1} - 2340 cm^{-1} (NH)

PMR characteristics (DMSO- D_6)

2.71 δ , (NMe, singlet); 5.08 δ , (can distinguish two hydroxyl groups)

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{ClNO}_2$: C, 52.08; H, 8.67; N, 6.74

Found: C, 52.44; H, 8.59; N, 6.70.

2- β -Benzylmethyl-3- β -Tropylbenzilate Hydrochloride (96a)

2 Hydroxymethyl-3- β -tropanol (3.0 g, 0.017 mole) was esterified with methyl benzilate (7.9 g, 0.035 mole) in the usual procedure to yield the ester free base (1.3 g, 11.0%) as a crude viscous oil. The oil was then treated with ether-HCl to yield the title compound in 89% yield, m.p. 127°C, from alcohol-ether.

IR spectrum:

ν_{\max} : 2780 cm^{-1} - 2290 cm^{-1} (NH), 1735 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

3.81 δ , (NMe, singlet); 7.36 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{37}\text{H}_{38}\text{ClNO}_6$: C, 70.77; H, 6.05; N, 2.22

Found: C, 70.55; H, 6.01; N, 2.21.

XI 1,2,5 —TRIMETHYL-4-PIPERIDINOL SYNTHESIS

Reduction of 1,2,5 —Trimethyl-4-Piperidone

1,2,5 —Trimethyl-4-piperidone (28.2 g, 0.15 mole) was reduced in the usual manner with lithium aluminium hydride (6.0 g, 0.15 mole) to yield the crude diastereoisomeric alcohol (28.0 g, 97%) as a viscous oil.

α -1,2,5 —Trimethyl-4-Piperidinol Hydrochloride (102)

The crude alcohol was treated with ether-HCl to yield the title compound in 98% yield. The solid was recrystallized from alcohol-ether to yield a crystalline solid which melted at 192-194°C (Narazov et al. reported 195-196°C). The picrate was also made, m.p. 141-143°C (Narazov et al., 1954, reported 142-143°C).

From the mother liquor no other crystalline solid was obtained. The free base was liberated from the mother liquor and the methiodide was made; however, a mixture of isomers was obtained (PMR evidence).

IR spectrum:

ν_{\max} : 3300 cm^{-1} (OH)

PMR characteristics (DMSO- D_6)

1.05 δ , 1.41 δ , (secondary Me groups, doublets);
2.86 δ , (NMe, singlet)

Anal. Calcd. for $\text{C}_8\text{H}_{18}\text{ClNO}$: C, 53.51; H, 10.02; N, 7.79

Found: C, 53.51; H, 10.01; N, 7.70.

1,2,5-Trimethyl-4-Piperidinol Methiodide (103)

The total crude alcohol (5.10 g, 0.035 mole) was treated with methyl iodide (14.0 g, 0.1 mole) in acetone (100 ml). The crude solid which precipitated was identified as a mixture of isomers, by PMR evidence. Fractional crystallization from absolute alcohol afforded one pure isomer, m.p. 260-263°C. From the mother liquor other fractions were obtained but these were also identified as mixtures of isomers.

IR spectrum:

ν_{\max} : 3400 cm^{-1} (OH)

PMR characteristics (DMSO- D_6)

0.93 and 1.30 δ (secondary Me groups, doublets);
3.08 δ (NMe_2 , doublet); 4.93 δ (OH, doublet)

Anal. Calcd. for $\text{C}_9\text{H}_{20}\text{INO}$: C, 37.92; H, 7.01; N, 4.91

Found: C, 37.82; H, 7.05; N, 4.83.

1,2,5-Trimethyl-4-Acetoxypiperidine Methiodide (104)

The crude alcohol (4.29 g, 0.023 mole) and acetyl chloride (7.9 g, 0.1 mole) were reacted in ethyl acetate (40 ml) in the usual manner for 8 hours to give 5 g (99%) of the acetoxy derivative as the hydrochloride. Fractional crystallization did not separate the isomers. The free base was liberated in the usual manner and the methiodide was made in the usual manner. Fractional crystallization from alcohol yielded one pure isomer, m.p. 204°C.

IR spectrum:

ν_{\max} : 1735 cm^{-1} (OH)

PMR characteristics (D_2O)

0.88 & 1.30 δ , (secondary methyl groups, doublets); 2.08 δ , (OMe, singlet); 3.10 δ , (NMe_2 , doublet); 4.65 δ , (C-4 methine proton, multiplet; base width 32 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{10}\text{H}_{22}\text{INO}_2$: C, 42.47; H, 7.07; N, 4.50

Found: C, 42.71; H, 7.00; N, 4.31.

1,2,5-Trimethyl-4-Piperidyl Benzilate (105)

The crude alcohol mixture (6.5 g, 0.045 mole) was esterified with methyl benzilate (10.8 g, 0.045 mole) by the usual procedure to yield 10.7 g (67%) of the title compound as a thick viscous oil which solidified on standing. After repeated recrystallization from alcohol-water one pure isomer, m.p. 137-138°C was obtained.

IR spectrum:

ν_{\max} : 3400 cm^{-1} (OH), 1740 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

0.60 & 1.31 δ , (secondary methyl groups, doublets);
2.18 δ , (NMe, singlet); 6.51 δ , (OH, singlet); 7.35 δ ,
(aromatic, singlet); 4.51 δ , (C-4 methine proton, base width
31 Hz, therefore axial proton)

Anal. Calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_3$: C, 74.8; H, 7.64

Found: C, 74.55; H, 7.96.

From the mother alcohol no other solid was obtained.

1,2,5-Trimethyl-4-Piperidyl Benzilate Hydrochloride (105a)

The crude ester was treated with ether-HCl to yield
the title compound in 98% yield. The solid obtained was
fractionally crystallized from alcohol-ether to yield one
pure isomer, m.p. 118-119°C.

IR spectrum:

ν_{\max} : 2700-2300 cm^{-1} (NH), 1730 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

0.61 & 1.31 δ , (secondary methyl groups, doublets);
2.65 δ , (NMe, singlet); 7.35 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{ClNO}_3$: C, 67.80; H, 7.18; N, 3.59

Found: C, 68.02; H, 7.15; N, 3.52.

From the mother liquor no other crystalline solid was
obtained.

1,2,5 -Trimethyl-4-Piperidyl Benzilate Methiodide (105b)

The methiodide was obtained in the usual manner in 89% yield. Fractional crystallization from alcohol yielded one pure isomer, m.p. 236-238°C.

IR spectrum:

ν_{\max} : 3390 cm^{-1} (OH), 1745 cm^{-1} (CO)

PMR characteristics (DMSO- D_6)

0.61 & 1.30 δ , (secondary methyl groups, doublets);
3.08 δ , (NMe_2 , doublet); 4.81 δ , (C-4 methine proton, base width 32 Hz, therefore axial proton); 6.51 δ , (OH, singlet);
7.40 δ , (aromatic, singlet)

Anal. Calcd. for $\text{C}_{23}\text{H}_{30}\text{INO}_3$: C, 55.78; H, 6.05; N, 2.82

Found: C, 55.67; H, 6.17; N, 2.90.

XII DIOXOLANE SYNTHESIS

2,2 -Diphenyl-4-Bromomethyl-1,3-Dioxolane (107)

Benzophenone (50 g, 0.27 mole), 45 g, (0.33 mole) of epibromohydrin and 250 ml of dry carbon tetrachloride were placed in a 500 ml, three-necked flask fitted with a stirrer, dropping funnel, and a thermometer. The mixture was stirred, cooled to 5°C and maintained at that temperature while a solution of 10 g, (0.038 mole) of stannic chloride in 75 ml of carbon tetrachloride was added, dropwise, during a three-hour period.. To the stirred orange-red solution was added 16 g of sodium hydroxide dissolved in 40 ml of water.

After 10 minutes the organic layer was separated, dried over anhydrous sodium carbonate, the solvent removed under reduced pressure, and the residue cooled in the refrigerator. After crystallization the product was recrystallized from absolute alcohol (64.5 g, 75%), m.p. 72-73°C (Blicke and Anderson, 1952, reported 71-73°C).

IR spectrum:

ν_{max} : 1660 cm^{-1} (C=C)

PMR characteristics

4.66 - 3.05 δ , (CH_2 , multiplet); 7.41 δ , (aromatic, multiplet)

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{BrO}_2$: C, 60.22; H, 4.70

Found: C, 59.89; H, 4.66.

2,2-Diphenyl-4-Benzylaminomethyl-1,3-Dioxolane

Hydrochloride (108a)

2,2-Diphenyl-4-bromomethyl-1,3-dioxolane (26.0 g, 0.081 mole), benzylamine (0.012 mole), and sodium carbonate (20 g, 0.2 mole) in benzene, 250 ml were stirred and heated under reflux for 8 hours. The suspension was then cooled and the sodium carbonate filtered off, and extracted with 10% HCl (3 X 100 ml). The aqueous layer was then basified with solid KOH and extracted with ether (5 X 100 ml). The ether was dried (Na_2SO_4) and evaporated to dryness. The benzylamine was azeotroped off with dry benzene. The hydrochloride was then made in the usual manner, and careful

fractional crystallization yielded (2.1 g, 7.0%) of the title compound, m.p. 215-217°C.

PMR characteristics (DMSO-D₆)

10.08 δ , (NH₂, singlet)

Anal. Calcd. for C₂₃H₂₄ClNO₂: C, 72.37; H, 6.28; N, 3.85

Found: C, 72.29; H, 6.16; N, 3.85.

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